

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**019908Orig1s032s034**

**021774Orig1s013s015**

***Trade Name:*** Ambien Tablets 5 and 10 mg  
Ambien CR Tablets 6.25 and 12.5 mg.

***Generic Name:*** Zolpidem tartrate  
Zolpidem tartrate extended-release

***Sponsor:*** Sanofi-Aventis US LLC

***Approval Date:*** April 19, 2013

# CENTER FOR DRUG EVALUATION AND RESEARCH

**019908Orig1s032s034**

**021774Orig1s013s015**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204447Orig1s000**

**APPROVAL LETTER**



**NDA 019908/S-032, S-034**  
**NDA 021774/S-013, S-015**

**SUPPLEMENT APPROVAL**

Sanofi-Aventis US LLC  
55 Corporate Drive  
Bridgewater, NJ 08807-5925

Attention: Doris Sincak, M.S.  
Project Supervisor, US Regulatory Affairs

Dear Ms. Sincak:

Please refer to your Supplemental New Drug Applications (sNDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ambien (zolpidem tartrate) Tablets 5 mg and 10 mg and Ambien CR (zolpidem tartrate extended-release) Tablets 6.25 and 12.5 mg.

<b>Application</b>	<b>Submitted on:</b>	<b>Received on:</b>	<b>Provides for:</b>
19908/ S-032	June 12, 2012	June 12, 2012	“Changes Being Effected” Supplement; Adverse Reactions: inclusion of lower respiratory infection, respiratory depression
21774/ S-013	June 12, 2012	June 12, 2012	“Changes Being Effected” Supplement; Adverse Reactions: inclusion of respiratory depression
19908/ S-034 21774/ S-015	April 4, 2013	April 4, 2013	FDAAA Safety Labeling Change Supplement: revisions to Dosage and Administration; Warnings and Precautions

We also refer to our letter dated January 9, 2013, notifying you, under Section 505(o)(4) of the FDCA, of new safety information to be included in the labeling for zolpidem tartrate. This information pertains to new dosing recommendations and safety warnings related to the risk of next-day psychomotor impairment.

In that letter, we notified you that the following sections of labeling should be revised based on that new safety information related to the risk of next-day psychomotor impairment: Recent Major Changes, Dosage and Administration, Drug Interactions, Use in Specific Populations, and Patient Counseling Information. The specific text for the Dosage and Administration section that we required at that time was as follows:

**Ambien (zolpidem tartrate tablets)**

**2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien should be individualized~~ Use the lowest dose effective for the patient.

**2.1 Dosage in adults**

~~The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Ambien dose should not exceed 10 mg per day. The recommended dose is 5 mg for women and either 5 or 10 mg for men. The 5 mg dose can be increased to 10 mg if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness. The recommended doses for women and men are different because women clear zolpidem from the body at a lower rate than men.~~

The total Ambien dose should not exceed 10 mg once daily immediately before bedtime.

**Ambien CR (zolpidem tartrate extended-release tablets)**

**2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien CR should be individualized.~~ Use the lowest dose effective for the patient.

**2.1 Dosage in adults**

~~The recommended dose of Ambien CR for adults is 12.5 mg once daily immediately before bedtime. The total Ambien CR dose should not exceed 12.5 mg per day. The recommended dose is 6.25 mg for women and either 6.25 or 12.5 mg for men. The 6.25 mg dose can be increased to 12.5 mg if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness. The recommended doses for women and men are different because women clear zolpidem from the body at a lower rate than men.~~

The total Ambien CR dose should not exceed 12.5 mg once daily immediately before bedtime.

However, following discussions with you and the subsequent receipt of your supplements (NDA 19908/S-034 and NDA 21774/S-015) dated April 4, 2013, the final agreed upon labeling text is:

### **Ambien (zolpidem tartrate tablets)**

## **2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien should be individualized~~

### **2.1 Dosage in Adults**

~~The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Ambien dose should not exceed 10 mg per day. Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [see Warnings and Precautions (5.1)]. The total dose of Ambien should not exceed 10 mg once daily immediately before bedtime.~~

~~The recommended initial doses for women and men are different because zolpidem clearance is lower in women.~~

### **Ambien CR (zolpidem tartrate extended-release tablets)**

## **2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien should be individualized~~

### **2.1 Dosage in Adults**

~~The recommended dose of Ambien CR for adults is 12.5 mg once daily immediately before bedtime. The total Ambien CR dose should not exceed 12.5 mg per day. Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [see Warnings and Precautions (5.1)]. The total dose of Ambien CR should not exceed 12.5 mg once daily immediately before bedtime.~~

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

We have completed our review of these supplemental applications. The applications are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package inserts, text for the and Medication Guides), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 019908/S-032, S-034  
NDA 021774/S-013, S-015  
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If you have any questions, call Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, M.D.  
Deputy Division Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling for NDA 19908, NDA 21774

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ERIC P BASTINGS  
04/19/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019908Orig1s032s034**

**021774Orig1s013s015**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN

### Ambien (zolpidem tartrate) tablets C-IV

Initial US Approval: 1992

#### -----RECENT MAJOR CHANGES-----

Dosage and Administration (2)	4/2013
Dosage and Administration, Dosage in Adults (2.1)	4/2013
Warnings and Precautions (5)	4/2013

#### -----INDICATIONS AND USAGE-----

Ambien, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

#### -----DOSAGE AND ADMINISTRATION-----

- Use the lowest dose effective for the patient (2.1)
- Recommended initial dose is 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening (2.1)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 5 mg for men and women (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with Ambien (2.3)
- The effect of Ambien may be slowed if taken with or immediately after a meal (2.4)

#### -----DOSAGE FORMS AND STRENGTHS-----

5 mg and 10 mg tablets. Tablets not scored. (3)

#### -----CONTRAINDICATIONS-----

Known hypersensitivity to zolpidem (4)

#### -----WARNINGS AND PRECAUTIONS-----

- CNS depressant effects: Impairs alertness and motor coordination. Instruct patients on correct use. (5.1)
- Need to evaluate for co-morbid diagnosis: Reevaluate if insomnia persists after 7 to 10 days of use. (5.2)

- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)
- “Sleep-driving” and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.5)
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function (5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation (5.7, 9.3)

#### -----ADVERSE REACTIONS-----

Most commonly observed adverse reactions were:

Short-term (< 10 nights): Drowsiness, dizziness, and diarrhea  
Long-term (28 - 35 nights): Dizziness and drugged feelings (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088, or <http://www.fda.gov/medwatch>

#### -----DRUG INTERACTIONS-----

- CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.1, 7.1)
- Imipramine: Decreased alertness observed (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
- Rifampin: Combination use may decrease effect (7.2)
- Ketoconazole: Combination use may increase effect (7.2)

#### -----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder (5.4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: xx/2013

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies [see *Clinical Studies (14)*].

The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [see *Warnings and Precautions (5.1)*]. The total dose of Ambien should not exceed 10 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

#### 2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of Ambien in both of these patient populations is 5 mg once daily immediately before bedtime [see *Warnings and Precautions (5.1); Use in Specific Populations (8.5)*].

#### 2.3 Use with CNS Depressants

Dosage adjustment may be necessary when Ambien is combined with other CNS depressant drugs because of the potentially additive effects [see *Warnings and Precautions (5.1)*].

#### 2.4 Administration

The effect of Ambien may be slowed by ingestion with or immediately after a meal.

### 3 DOSAGE FORMS AND STRENGTHS

Ambien is available in 5 mg and 10 mg strength tablets for oral administration. Tablets are not scored.

Ambien 5 mg tablets are capsule-shaped, pink, film coated, with AMB 5 debossed on one side and 5401 on the other.

Ambien 10 mg tablets are capsule-shaped, white, film coated, with AMB 10 debossed on one side and 5421 on the other.

#### **4 CONTRAINDICATIONS**

Ambien is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions include anaphylaxis and angioedema [see *Warnings and Precautions (5.3)*].

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 CNS Depressant Effects and Next-Day Impairment**

Ambien, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustments of Ambien and of other concomitant CNS depressants may be necessary when Ambien is administered with such agents because of the potentially additive effects. The use of Ambien with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended [see *Dosage and Administration (2.3)*].

The risk of next-day psychomotor impairment, including impaired driving, is increased if Ambien is taken with less than a full night of sleep remaining (7- to 8 hours); if a higher than the recommended dose is taken; if co-administered with other CNS depressants; or if co-administered with other drugs that increase the blood levels of zolpidem. Patients should be cautioned against driving and other activities requiring complete mental alertness if Ambien is taken in these circumstances [see *Dosage and Administration (2)* and *Clinical Studies (14.3)*].

##### **5.2 Need to Evaluate for Co-morbid Diagnoses**

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem.

##### **5.3 Severe Anaphylactic and Anaphylactoid Reactions**

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

##### **5.4 Abnormal Thinking and Behavioral Changes**

Abnormal thinking and behavior changes have been reported in patients treated with sedative/hypnotics, including Ambien. Some of these changes included decreased inhibition

(e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials of Ambien 10 mg taken at bedtime < 1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with Ambien 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [see *Use in Specific Populations* (8.4)].

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” have occurred with Ambien alone at therapeutic doses, the co-administration of Ambien with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of Ambien at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien should be strongly considered for patients who report a “sleep-driving” episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may also occur.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

### **5.5 Use in Patients with Depression**

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

### **5.6 Respiratory Depression**

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Ambien is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risk of respiratory depression should be considered prior to prescribing Ambien in patients with respiratory impairment including sleep apnea and myasthenia gravis.

## 5.7 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence [see *Drug Abuse and Dependence (9.2) and (9.3)*].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- CNS-depressant effects and next-day impairment [see *Warnings and Precautions (5.1)*]
- Serious anaphylactic and anaphylactoid reactions [see *Warnings and Precautions (5.3)*]
- Abnormal thinking and behavior changes, and complex behaviors [see *Warnings and Precautions (5.4)*]
- Withdrawal effects [see *Warnings and Precautions (5.7)*]

### 6.1 Clinical Trials Experience

**Associated with discontinuation of treatment:** Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

**Most commonly observed adverse reactions in controlled trials:** During short-term treatment (up to 10 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

**Adverse reactions observed at an incidence of  $\geq 1\%$  in controlled trials:** The following tables enumerate treatment-emergent adverse reactions frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate

and at a greater incidence than placebo in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from results of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

**Incidence of Treatment-Emergent Adverse Experiences in  
Placebo-Controlled Clinical Trials Lasting up to 10 Nights**  
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	-

\*Reactions reported by at least 1% of patients treated with Ambien and at a greater frequency than placebo.

The following table was derived from results of three placebo-controlled long-term efficacy trials involving Ambien (zolpidem tartrate). These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

**Incidence of Treatment-Emergent Adverse Experiences in  
Placebo-Controlled Clinical Trials Lasting up to 35 Nights**  
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1

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Body as a Whole		
Allergy	4	1
Back Pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-
Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

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\*Reactions reported by at least 1% of patients treated with Ambien and at a greater frequency than placebo.

**Dose relationship for adverse reactions:** There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

**Adverse event incidence across the entire preapproval database:** Ambien was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion

while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Ambien, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

**Autonomic nervous system:** Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

**Body as a whole:** Frequent: asthenia. Infrequent: edema, falling, fatigue, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

**Cardiovascular system:** Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

**Central and peripheral nervous system:** Frequent: ataxia, confusion, euphoria, headache, insomnia, vertigo. Infrequent: agitation, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

**Gastrointestinal system:** Frequent: dyspepsia, hiccup, nausea. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

**Hematologic and lymphatic system:** Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

**Immunologic system:** Infrequent: infection. Rare: abscess herpes simplex herpes zoster, otitis externa, otitis media.

**Liver and biliary system:** Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

**Metabolic and nutritional:** Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

**Musculoskeletal system:** Frequent: arthralgia, myalgia. Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

**Reproductive system:** Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

**Respiratory system:** Frequent: upper respiratory infection, lower respiratory infection. Infrequent: bronchitis, coughing, dyspnea, rhinitis. Rare: bronchospasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

**Skin and appendages:** Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

**Special senses:** Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

**Urogenital system:** Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

## 7 DRUG INTERACTIONS

### 7.1 CNS-active Drugs

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [see *Warnings and Precautions (5.1)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

#### *Imipramine, Chlorpromazine*

Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance [see *Clinical Pharmacology (12.3)*].

#### *Haloperidol*

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration [see *Clinical Pharmacology (12.3)*].

### *Alcohol*

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (5.1)*].

### *Sertraline*

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem [see *Clinical Pharmacology (12.3)*].

### *Fluoxetine*

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance [see *Clinical Pharmacology (12.3)*].

## **7.2 Drugs that Affect Drug Metabolism via Cytochrome P450**

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of drugs on other P450 enzymes on the exposure to zolpidem is not known.

### *Rifampin*

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of Rifampin in combination with zolpidem may decrease the efficacy of zolpidem.

### *Ketoconazole*

Ketoconazole, a potent CYP3A4 inhibitor, increased the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Category C*

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

Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS-depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. Ambien should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the Ambien maximum recommended human dose (MRHD) of 10 mg/day (approximately 8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m<sup>2</sup> basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/m<sup>2</sup> basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m<sup>2</sup> basis.

## 8.2 Labor and Delivery

Ambien has no established use in labor and delivery [*see Pregnancy (8.1)*].

## 8.3 Nursing Mothers

Zolpidem is excreted in human milk. Caution should be exercised when Ambien is administered to a nursing woman.

## 8.4 Pediatric Use

Ambien is not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

In an 8-week study, in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [*see Warnings and Precautions(5.4)*]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

## 8.5 Geriatric Use

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥ 60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

<b>Adverse Event</b>	<b>Zolpidem</b>	<b>Placebo</b>
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem

doses >10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were  $\geq$  70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

The dose of Ambien in elderly patients is 5 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see *Warnings and Precautions (5.1)*].

## **8.6 Gender Difference in Pharmacokinetics**

Women clear zolpidem tartrate from the body at a lower rate than men.  $C_{max}$  and AUC parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of Ambien for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of Ambien in geriatric patients is 5 mg regardless of gender.

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

### **9.2 Abuse**

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

### **9.3 Dependence**

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence and withdrawal have been received.

## **10 OVERDOSAGE**

### **10.1 Signs and Symptoms**

In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

### **10.2 Recommended Treatment**

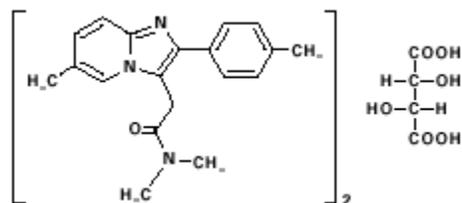
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdose, even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

## **11 DESCRIPTION**

Ambien (zolpidem tartrate) is a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class and is available in 5 mg and 10 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ<sub>1</sub> receptor preferentially with a high affinity ratio of the  $\alpha_1/\alpha_5$  subunits. This selective binding of zolpidem on the BZ<sub>1</sub> receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

### 12.3 Pharmacokinetics

The pharmacokinetic profile of Ambien is characterized by rapid absorption from the gastrointestinal tract and a short elimination half-life ( $T_{1/2}$ ) in healthy subjects.

In a single-dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations ( $C_{max}$ ) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time ( $T_{max}$ ) of 1.6 hours for both. The mean Ambien elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. Ambien is converted to inactive metabolites that are eliminated primarily by renal excretion. Ambien demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be  $92.5 \pm 0.1\%$  and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

A food-effect study in 30 healthy male subjects compared the pharmacokinetics of Ambien 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and  $C_{\max}$  were decreased by 15% and 25%, respectively, while mean  $T_{\max}$  was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, Ambien should not be administered with or immediately after a meal.

### ***Special Populations***

#### ***Elderly:***

In the elderly, the dose for Ambien should be 5 mg [*see Warnings and Precautions (5) and Dosage and Administration (2)*]. This recommendation is based on several studies in which the mean  $C_{\max}$ ,  $T_{1/2}$ , and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (> 70 years), the means for  $C_{\max}$ ,  $T_{1/2}$ , and AUC significantly increased by 50% (255 vs. 384 ng/mL), 32% (2.2 vs. 2.9 hr), and 64% (955 vs. 1,562 ng·hr/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20 mg oral dose. Ambien did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

#### ***Hepatic Impairment:***

The pharmacokinetics of Ambien in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean  $C_{\max}$  and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically -compromised patients.  $T_{\max}$  did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency [*see Dosage and Administration (2.2)*].

#### ***Renal Impairment:***

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean  $Cl_{Cr}$  =  $6.5 \pm 1.5$  mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for  $C_{\max}$ ,  $T_{\max}$ , half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

### **Drug Interactions**

#### ***CNS-depressants***

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [*see Warnings and Precautions (5.1)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [*see Warnings and Precautions (5.1)*].

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem  $C_{\max}$  was significantly higher (43%) and  $T_{\max}$  was significantly decreased (-53%). Pharmacokinetics of sertraline and N-desmethylertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

#### *Drugs that Affect Drug Metabolism via Cytochrome P450*

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in  $AUC_{0-\infty}$  of zolpidem tartrate. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (-73%),  $C_{\max}$  (-58%), and  $T_{1/2}$  (-36 %) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased  $C_{\max}$  of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30 %) along with an increase in the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

#### *Other Drugs with No Interactions with Zolpidem*

A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenesis:* Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg. In mice, these doses are approximately 2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m<sup>2</sup> basis. In rats, these doses are approximately 5, 20, and 100 times the MRHD on a mg/m<sup>2</sup> basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

*Mutagenesis:* Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

*Impairment of fertility:* Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 24 times the MRHD on a mg/m<sup>2</sup> basis. There was no impairment of fertility at any dose tested.

## 14 CLINICAL STUDIES

### 14.1 Transient Insomnia

Normal adults experiencing transient insomnia (n = 462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n = 35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

### 14.2 Chronic Insomnia

Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n = 75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was

superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week.

Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with Ambien.

### **14.3 Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs**

*Next-day residual effects:* Next-day residual effects of Ambien were evaluated in seven studies involving normal subjects. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of Ambien in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

*Rebound effects:* There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of Ambien (zolpidem tartrate). There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

*Memory impairment:* Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of Ambien. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose), i.e., these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of Ambien, predominantly at doses above 10 mg.

*Effects on sleep stages:* In studies that measured the percentage of sleep time spent in each sleep stage, Ambien has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Ambien 5 mg tablets are capsule-shaped, pink, film coated, with AMB 5 debossed on one side and 5401 on the other and supplied as:

<b><u>NDC Number</u></b>	<b><u>Size</u></b>
0024-5401-31	bottle of 100

Ambien 10 mg tablets are capsule-shaped, white, film coated, with AMB 10 debossed on one side and 5421 on the other and supplied as:

<b><u>NDC Number</u></b>	<b><u>Size</u></b>
0024-5421-31	bottle of 100
0024-5421-50	bottle of 500

Store at controlled room temperature 20°–25°C (68°–77°F).

## **17 PATIENT COUNSELING INFORMATION**

*See FDA-approved patient labeling (Medication Guide).*

Inform patients and their families about the benefits and risks of treatment with Ambien. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with Ambien and with each prescription refill. Review the Ambien Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that Ambien should be taken only as prescribed.

### *CNS Depressant Effects and Next-Day Impairment*

Tell patients that Ambien has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness. Inform patients that impairment can be present despite feeling fully awake.

### *Severe Anaphylactic and Anaphylactoid Reactions*

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

### *Sleep-driving and Other Complex Behaviors*

Instruct patients and their families that sedative hypnotics can cause abnormal thinking and behavior change, including “sleep driving” and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex). Tell patients to call you immediately if they develop any of these symptoms.

### *Suicide*

Tell patients to immediately report any suicidal thoughts.

### *Alcohol and Other Drugs*

Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use Ambien if they drank alcohol that evening or before bed.

### *Tolerance, Abuse, and Dependence*

Tell patients not to increase the dose of Ambien on their own, and to inform you if they believe the drug “does not work”.

### *Administration Instructions*

Patients should be counseled to take Ambien right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Ambien tablets should not be taken with or immediately after a meal. Advise patients NOT to take Ambien if they drank alcohol that evening.

**MEDICATION GUIDE**  
**AMBIEN®** (ām' bē-ən)  
(zolpidem tartrate)  
**Tablets C-IV**

Read the Medication Guide that comes with AMBIEN before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

**What is the most important information I should know about AMBIEN?**

- **Do not take more AMBIEN than prescribed.**
- **Do not take AMBIEN unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take AMBIEN right before you get in bed, not sooner.**

**AMBIEN may cause serious side effects, including:**

- **After taking AMBIEN, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night.** You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with AMBIEN. Reported activities include:
  - driving a car ("sleep-driving")
  - making and eating food
  - talking on the phone
  - having sex
  - sleep-walking

**Call your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN.**

**Do not take AMBIEN if you:**

- drank alcohol that evening or before bed
- took another medicine to help you sleep

**What is AMBIEN?**

AMBIEN is a sedative-hypnotic (sleep) medicine. AMBIEN is used in adults for the short-term treatment of a sleep problem called insomnia (trouble falling asleep).

It is not known if AMBIEN is safe and effective in children under the age of 18 years.

AMBIEN is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep AMBIEN in a safe place to prevent misuse and abuse. Selling or giving away AMBIEN may harm others, and is against the law. Tell your healthcare provider if you have ever abused or have been dependent on alcohol, prescription medicines or street drugs.

**Who should not take AMBIEN?**

- Do not take AMBIEN if you are allergic to zolpidem or any other ingredients in AMBIEN. See the end of this Medication Guide for a complete list of ingredients in AMBIEN.
- Do not take AMBIEN if you have had an allergic reaction to drugs containing zolpidem, such as Ambien CR, Edluar, Zolpimist, or Intermezzo.

Symptoms of a serious allergic reaction to zolpidem can include:

- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

**What should I tell my healthcare provider before taking AMBIEN?**

**AMBIEN may not be right for you. Before starting AMBIEN, tell your healthcare provider about all of your health conditions, including if you:**

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems

- are pregnant, planning to become pregnant. It is not known if AMBIEN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. AMBIEN can pass into your breast milk. It is not known if AMBIEN will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN.

**Tell your healthcare provider about all of the medicines you take**, including prescription and nonprescription medicines, vitamins and herbal supplements.

Medicines can interact with each other, sometimes causing serious side effects. **Do not take AMBIEN with other medicines that can make you sleepy unless your healthcare provider tells you to.**

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

#### **How should I take AMBIEN?**

- See **“What is the most important information I should know about AMBIEN?”**
- Take AMBIEN exactly as prescribed. Only take 1 AMBIEN tablet a night if needed.
- Do not take AMBIEN if you drank alcohol that evening or before bed.
- You should not take AMBIEN with or right after a meal. AMBIEN may help you fall asleep faster if you take it on an empty stomach.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- If you take too much AMBIEN or overdose, get emergency treatment.

#### **What are the possible side effects of AMBIEN?**

**AMBIEN may cause serious side effects, including:**

- **getting out of bed while not being fully awake and do an activity that you do not know you are doing.** See **“What is the most important information I should know about AMBIEN?”**
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations,

worsening of depression, and suicidal thoughts or actions.

- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, and trouble breathing. Get emergency medical help if you get these symptoms after taking AMBIEN.

**Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using AMBIEN.**

**The most common side effects of AMBIEN are:**

- drowsiness
- dizziness
- diarrhea
- grogginess or feeling as if you have been drugged

**After you stop taking a sleep medicine,** you may have symptoms for 1 to 2 days such as:

- trouble sleeping
- nausea
- flushing
- lightheadedness
- uncontrolled crying
- vomiting
- stomach cramps
- panic attack
- nervousness
- stomach area pain

These are not all the side effects of AMBIEN. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

#### **How should I store AMBIEN?**

- Store AMBIEN at room temperature, 68°F to 77°F (20°C to 25°C).

**Keep AMBIEN and all medicines out of reach of children.**

## **General Information about the safe and effective use of AMBIEN**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMBIEN for a condition for which it was not prescribed. Do not share AMBIEN with other people, even if they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about AMBIEN. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMBIEN that is written for healthcare professionals.

For more information, call 1-800-633-1610.

### **What are the ingredients in AMBIEN?**

**Active Ingredient:** Zolpidem tartrate

**Inactive Ingredients:** hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. In addition, the 5 mg tablet contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807  
A SANOFI COMPANY

Month 2013

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use

Ambien CR safely and effectively. See full prescribing information for Ambien CR.

### Ambien CR (zolpidem tartrate extended-release) tablets C-IV

Initial U.S. Approval: 1992

#### RECENT MAJOR CHANGES

Dosage and Administration (2)	4/2013
Dosage and Administration, Dosage in Adults (2.1)	4/2013
Warnings and Precautions (5)	4/2013

#### INDICATIONS AND USAGE

Ambien CR, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

#### DOSAGE AND ADMINISTRATION

- Use the lowest dose effective for the patient (2.1)
- Recommended initial dose is 6.25 mg for women, and 6.25 or 12.5 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening (2.1)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 6.25 mg for men and women (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with Ambien CR (2.3)
- Tablets to be swallowed whole, not to be crushed, divided or chewed (2.4)
- The effect of Ambien CR may be slowed if taken with or immediately after a meal (2.4)

#### DOSAGE FORMS AND STRENGTHS

Tablets: 6.25 mg and 12.5 mg extended-release tablets. Tablets not scored. (3)

#### CONTRAINDICATIONS

Known hypersensitivity to zolpidem (4)

#### WARNINGS AND PRECAUTIONS

- CNS depressant effects: Impaired alertness and motor coordination, including risk of morning impairment. Caution patients against driving and other activities requiring complete mental alertness the morning after use. (5.1)

- Need to evaluate for co-morbid diagnoses: Reevaluate if insomnia persists after 7 to 10 days of use (5.2)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)
- "Sleep-driving" and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.5)
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function (5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation (5.7, 9.3)

#### ADVERSE REACTIONS

Most commonly observed adverse reactions (> 10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

#### DRUG INTERACTIONS

- CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.1, 7.1)
- Imipramine: Decreased alertness observed (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
- Rifampin: Combination use may decrease effect (7.2)
- Ketoconazole: Combination use may increase effect (7.2)

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm (8.1)
- Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder (5.4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised Month/2013

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) in duration [*see Clinical Studies (14)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [*see Warnings and Precautions (5.1)*]. The total dose of Ambien CR should not exceed 12.5 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

#### 2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of Ambien CR in both of these patient populations is 6.25 mg once daily immediately before bedtime [*see Warnings and Precautions (5.1); Use in Specific Populations (8.5)*].

#### 2.3 Use with CNS Depressants

Dosage adjustment may be necessary when Ambien CR is combined with other CNS depressant drugs because of the potentially additive effects [*see Warnings and Precautions (5.1)*].

#### 2.4 Administration

Ambien CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of Ambien CR may be slowed by ingestion with or immediately after a meal.

### 3 DOSAGE FORMS AND STRENGTHS

Ambien CR is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

Ambien CR 6.25 mg tablets are pink, round, bi-convex, and debossed with A~ on one side.

Ambien CR 12.5 mg tablets are blue, round, bi-convex, and debossed with A~ on one side.

#### **4 CONTRAINDICATIONS**

Ambien CR is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions include anaphylaxis and angioedema [*see Warnings and Precautions (5.3)*].

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 CNS Depressant Effects and Next-Day Impairment**

Ambien CR is a central nervous system (CNS) depressant and can impair daytime function in some patients even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e. less than formal psychomotor testing). While pharmacodynamic tolerance or adaptation to some adverse depressant effects of Ambien CR may develop, patients using Ambien CR should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.

Additive effects occur with concomitant use of other CNS depressants (e.g. benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use. Downward dose adjustment of Ambien CR and concomitant CNS depressants should be considered [*see Dosage and Administration (2.3)*].

The use of Ambien CR with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if Ambien CR is taken with less than a full night of sleep remaining (7- to 8 hours); if higher than the recommended dose is taken; if co-administered with other CNS depressants; or co-administered with other drugs that increase the blood levels of zolpidem [*see Dosage and Administration (2) and Clinical Studies (14.2)*].

##### **5.2 Need to Evaluate for Co-morbid Diagnoses**

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem.

### **5.3 Severe Anaphylactic and Anaphylactoid Reactions**

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

### **5.4 Abnormal Thinking and Behavioral Changes**

Abnormal thinking and behavior changes have been reported in patients treated with sedative/hypnotics, including Ambien CR. Some of these changes included decreased inhibition (e.g. aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials, <1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with Ambien 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [*see Use in Specific Populations (8.4)*].

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” have occurred with Ambien CR alone at therapeutic doses, the co-administration of alcohol and other CNS depressants increases the risk of such behaviors, as does the use of Ambien CR at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien CR should be strongly considered for patients who report a “sleep-driving” episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may also occur.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

### **5.5 Use in Patients with Depression**

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

## 5.6 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Ambien CR is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risk of respiratory depression should be considered prior to prescribing Ambien CR in patients with respiratory impairment including sleep apnea and myasthenia gravis.

## 5.7 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence [*see Drug Abuse and Dependence (9.2) and (9.3)*].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- CNS-depressant effects and next-day impairment [*see Warnings and Precautions (5.1)*]
- Serious anaphylactic and anaphylactoid reactions [*see Warnings and Precautions (5.3)*]
- Abnormal thinking and behavior changes, and complex behaviors [*see Warnings and Precautions (5.4)*]
- Withdrawal effects [*see Warnings and Precautions (5.7)*]

### 6.1 Clinical Trials Experience

**Associated with discontinuation of treatment:** In 3-week clinical trials in adults and elderly patients (> 65 years), 3.5% (7/201) patients receiving Ambien CR 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.9% (2/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with Ambien CR was somnolence (1%).

In a 6-month study in adult patients (18-64 years of age), 8.5% (57/669) of patients receiving Ambien CR 12.5 mg as compared to 4.6% on placebo (16/349) discontinued treatment due to an adverse reaction. Reactions most commonly associated with discontinuation of Ambien CR included anxiety (anxiety, restlessness or agitation) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo, and depression (depression, major depression or depressed mood) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo.

Data from a clinical study in which selective serotonin reuptake inhibitor- (SSRI-) treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or

aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

**Most commonly observed adverse reactions in controlled trials:** During treatment with Ambien CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of Ambien CR were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating Ambien CR 12.5 mg, the adverse reaction profile was consistent with that reported in short-term trials, except for a higher incidence of anxiety (6.3% for Ambien CR versus 2.6% for placebo).

**Adverse reactions observed at an incidence of  $\geq 1\%$  in controlled trials:** The following tables enumerate treatment-emergent adverse reaction frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following tables were derived from results of two placebo-controlled efficacy trials involving Ambien CR. These trials involved patients with primary insomnia who were treated for 3 weeks with Ambien CR at doses of 12.5 mg (Table 1) or 6.25 mg (Table 2), respectively. The tables include only adverse reactions occurring at an incidence of at least 1% for Ambien CR patients and with an incidence greater than that seen in the placebo patients.

<b>Table 1. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Adults (percentage of patients reporting)</b>		
<b>Body System/Adverse Reaction *</b>	<b>Ambien CR 12.5 mg (N = 102)</b>	<b>Placebo (N = 110)</b>
<b>Infections and infestations</b>		
Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
<b>Metabolism and nutrition disorders</b>		
Appetite disorder	1	0
<b>Psychiatric disorders</b>		
Hallucinations **	4	0
Disorientation	3	2

Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0
Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
<b>Nervous system disorders</b>		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders ***	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
<b>Eye disorders</b>		
Visual disturbance	3	0
Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
<b>Ear and labyrinth disorders</b>		
Vertigo	2	0
Tinnitus	1	0
<b>Respiratory, thoracic and mediastinal disorders</b>		
Throat irritation	1	0
<b>Gastrointestinal disorders</b>		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux disease	1	0
Vomiting	1	0
<b>Skin and subcutaneous tissue disorders</b>		
Rash	1	0
Skin wrinkling	1	0
Urticaria	1	0
<b>Musculoskeletal and connective tissue disorders</b>		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0

<b>Reproductive system and breast disorders</b>		
Menorrhagia	1	0
<b>General disorders and administration site conditions</b>		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
<b>Investigations</b>		
Blood pressure increased	1	0
Body temperature increased	1	0
<b>Injury, poisoning and procedural complications</b>		
Contusion	1	0
<b>Social circumstances</b>		
Exposure to poisonous plant	1	0

\*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.

\*\*Hallucinations included hallucinations NOS as well as visual and hypnagogic hallucinations.

\*\*\*Memory disorders include: memory impairment, amnesia, anterograde amnesia.

<b>Table 2. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Elderly (percentage of patients reporting)</b>		
<b>Body System/Adverse Reaction *</b>	<b>Ambien CR 6.25 mg (N=99)</b>	<b>Placebo (N=106)</b>
<b>Infections and infestations</b>		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
<b>Psychiatric disorders</b>		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
<b>Nervous system disorders</b>		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders **	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0

<b>Cardiac disorders</b>		
Palpitations	2	0
<b>Respiratory, thoracic and mediastinal disorders</b>		
Dry throat	1	0
<b>Gastrointestinal disorders</b>		
Flatulence	1	0
Vomiting	1	0
<b>Skin and subcutaneous tissue disorders</b>		
Rash	1	0
Urticaria	1	0
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
<b>Renal and urinary disorders</b>		
Dysuria	1	0
<b>Reproductive system and breast disorders</b>		
Vulvovaginal dryness	1	0
<b>General disorders and administration site conditions</b>		
Influenza like illness	1	0
Pyrexia	1	0
<b>Injury, poisoning and procedural complications</b>		
Neck injury	1	0

\*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.

\*\*Memory disorders include: memory impairment, amnesia, anterograde amnesia.

***Dose relationship for adverse reactions:*** There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

***Other adverse reactions observed during the premarketing evaluation of Ambien CR:*** Other treatment-emergent adverse reactions associated with participation in Ambien CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

***Adverse Events Observed During the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate:***

Immediate-release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Ambien, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

***Autonomic nervous system:*** Frequent: dry mouth. Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

***Body as a whole:*** Frequent: asthenia. Infrequent: chest pain, edema, falling, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

***Cardiovascular system:*** Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

***Central and peripheral nervous system:*** Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, insomnia, lethargy, lightheadedness, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

**Gastrointestinal system:** Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

**Hematologic and lymphatic system:** Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

**Immunologic system:** Infrequent: infection. Rare: abscess herpes simplex herpes zoster, otitis externa, otitis media.

**Liver and biliary system:** Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

**Metabolic and nutritional:** Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

**Musculoskeletal system:** Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

**Reproductive system:** Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

**Respiratory system:** Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

**Skin and appendages:** Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

**Special senses:** Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

**Urogenital system:** Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

## **7 DRUG INTERACTIONS**

### **7.1 CNS-active Drugs**

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [see *Warnings and Precautions (5.1)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

#### *Imipramine, Chlorpromazine*

Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic

interaction, but there was an additive effect of decreased alertness and psychomotor performance [see *Clinical Pharmacology (12.3)*].

#### *Haloperidol*

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration [see *Clinical Pharmacology (12.3)*].

#### *Alcohol*

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (5.1)*].

#### *Sertraline*

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem [see *Clinical Pharmacology (12.3)*].

#### *Fluoxetine*

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance [see *Clinical Pharmacology (12.3)*].

## **7.2 Drugs that Affect Drug Metabolism via Cytochrome P450**

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of drugs on other P450 enzymes on the exposure to zolpidem is not known.

#### *Rifampin*

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of Rifampin in combination with zolpidem may decrease the efficacy of zolpidem.

#### *Ketoconazole*

Ketoconazole, a potent CYP3A4 inhibitor, increased the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Category C*

There are no adequate and well-controlled studies of Ambien CR in pregnant women. Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. Ambien CR should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the Ambien CR maximum recommended human dose (MRHD) of 12.5 mg/day (approximately 10 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m<sup>2</sup> basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day, increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 8 times the MRHD on a mg/m<sup>2</sup> basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m<sup>2</sup> basis.

## **8.2 Labor and Delivery**

Ambien CR has no established use in labor and delivery [*see Pregnancy (8.1)*].

## **8.3 Nursing Mothers**

Zolpidem is excreted in human milk. Caution should be exercised when Ambien CR is administered to a nursing woman.

## **8.4 Pediatric Use**

Ambien CR is not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [*see Warnings and Precautions (5.4)*]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

FDA has not required pediatric studies of Ambien CR in the pediatric population based on these efficacy and safety findings.

## 8.5 Geriatric Use

A total of 99 elderly ( $\geq 65$  years of age) received daily doses of 6.25 mg Ambien CR in a 3-week placebo-controlled study. The adverse reaction profile of Ambien CR 6.25 mg in this population was similar to that of Ambien CR 12.5 mg in younger adults ( $\leq 64$  years of age). Dizziness was reported in 8% of Ambien CR-treated patients compared with 3% of those treated with placebo.

The dose of Ambien CR in elderly patients is 6.25 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see *Warnings and Precautions (5.1)*].

## 8.6 Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men.  $C_{\max}$  and AUC parameters of zolpidem from Ambien CR were, respectively, approximately 50% and 75% higher at the same dose in adult female subjects compared to adult male subjects. Between 6 and 12 hours after dosing, zolpidem concentrations were 2- to 3 fold higher in adult female compared to adult male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of Ambien CR for adult women is 6.25 mg, and the recommended dose for adult men is 6.25 or 12.5 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of Ambien CR in geriatric patients is 6.25 mg regardless of gender.

# 9 DRUG ABUSE AND DEPENDENCE

## 9.1 Controlled Substance

Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

## 9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg effects were difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

### **9.3 Dependence**

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events, which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal, were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence and withdrawal have been received.

## **10 OVERDOSAGE**

### **10.1 Signs and Symptoms**

In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise and fatal outcomes have been reported.

### **10.2 Recommended Treatment**

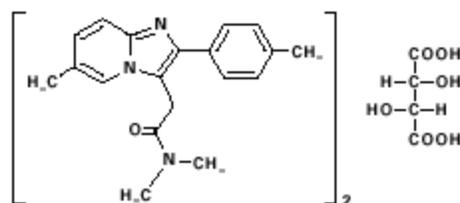
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdose, even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

## 11 DESCRIPTION

Ambien CR contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class. Ambien CR (zolpidem tartrate extended-release tablets) is available in 6.25 mg and 12.5 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Ambien CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The 6.25 mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide. The 12.5 mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

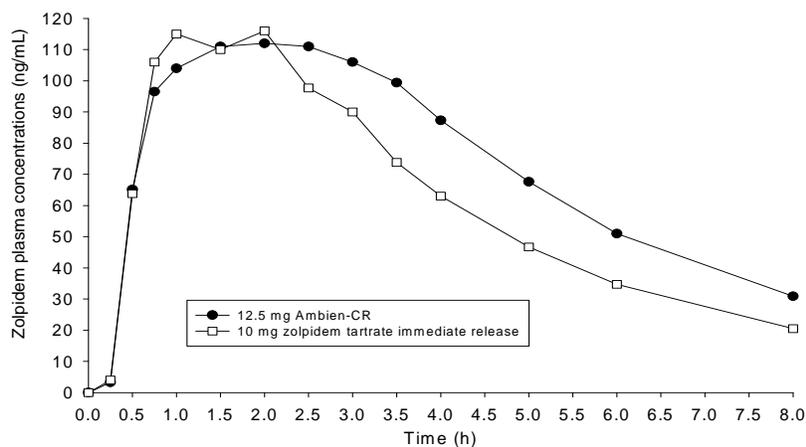
Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ<sub>1</sub> receptor preferentially with a high affinity ratio of the  $\alpha_1/\alpha_5$  subunits. This selective binding of zolpidem on the BZ<sub>1</sub> receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

### 12.3 Pharmacokinetics

Ambien CR exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides

extended plasma concentrations beyond three hours after administration. A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of Ambien CR 12.5 mg and of an immediate-release formulation of zolpidem tartrate (10 mg). The terminal elimination half-life observed with Ambien CR (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg). The mean plasma concentration-time profiles are shown in Figure 1.

**Figure 1: Mean plasma concentration-time profiles for Ambien CR (12.5 mg) and immediate-release zolpidem tartrate (10 mg)**



In adult and elderly patients treated with Ambien CR, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

#### *Absorption:*

Following administration of Ambien CR, administered as a single 12.5 mg dose in healthy male adult subjects, the mean peak concentration ( $C_{max}$ ) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/ml) occurring at a median time ( $T_{max}$ ) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy subjects compared the pharmacokinetics of Ambien CR 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and  $C_{max}$  were decreased by 23% and 30%, respectively, while median  $T_{max}$  was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, Ambien CR should not be administered with or immediately after a meal.

#### *Distribution:*

Total protein binding was found to be  $92.5 \pm 0.1\%$  and remained constant, independent of concentration between 40 and 790 ng/mL.

*Metabolism:*

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

*Elimination:*

When Ambien CR was administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

*Special Populations*

*Elderly:*

In 24 elderly ( $\geq 65$  years) healthy subjects administered a single 6.25 mg dose of Ambien CR, the mean peak concentration ( $C_{\max}$ ) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time ( $T_{\max}$ ) of 2.0 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

*Hepatic Impairment:*

Ambien CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean  $C_{\max}$  and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients.  $T_{\max}$  did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency [*see Dosage and Administration (2.2)*].

*Renal Impairment:*

Ambien CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean  $Cl_{Cr} = 6.5 \pm 1.5$  mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for  $C_{\max}$ ,  $T_{\max}$ , half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally-impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

## Drug Interactions

### *CNS-depressants*

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [see *Warnings and Precautions (5.1)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (5.1)*].

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem  $C_{max}$  was significantly higher (43%) and  $T_{max}$  was significantly decreased (-53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

### *Drugs that Affect Drug Metabolism via Cytochrome P450*

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in  $AUC_{0-\infty}$  of zolpidem tartrate. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (-73%),  $C_{max}$  (-58%), and  $T_{1/2}$  (-36 %) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased  $C_{max}$  of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30 %) along with an increase in the pharmacodynamic effects of zolpidem. Consideration

should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

#### *Other Drugs with No Interactions with Zolpidem*

A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Carcinogenesis:* Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg. In mice, these doses are approximately 2, 9, and 40 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) on mg/m<sup>2</sup> basis. In rats, these doses are approximately 4, 18, and 80 times the MRHD on a mg/m<sup>2</sup> basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

*Mutagenesis:* Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

*Impairment of fertility:* Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 20 times the MRHD on a mg/m<sup>2</sup> basis. There was no impairment of fertility at any dose tested.

## **14 CLINICAL STUDIES**

### **14.1 Controlled Clinical Trials**

Ambien CR was evaluated in three placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

Adult outpatients (18-64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo. Ambien CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Ambien CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment. Ambien CR 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

Elderly outpatients ( $\geq 65$  years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Ambien CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment. Ambien CR 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, in patients treated with Ambien CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

In a 24-week double-blind, placebo controlled, randomized study in adult outpatients (18-64 years) with primary insomnia (N=1025), Ambien CR 12.5 mg administered as needed (3 to 7 nights per week) was superior to placebo over 24 weeks, on patient global impression regarding aid to sleep, and on patient-reported specific sleep parameters for sleep induction and sleep maintenance with no significant increased frequency of drug intake observed over time.

#### **14.2 Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs**

**Next-day residual effects:** In five clinical studies [three controlled studies in adults (18-64 years of age) administered Ambien CR 12.5 mg and two controlled studies in the elderly ( $\geq 65$  years of age) administered Ambien CR 6.25 mg or 12.5 mg], the effect of Ambien CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with Ambien CR 12.5 mg and 6.25 mg using self-ratings of sedation.

During the 3-week studies, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg Ambien CR versus 2% of the placebo group; next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg Ambien CR versus 5% of the placebo group [see *Adverse Reactions (6)*]. In a 6-month study, the overall incidence of next-day somnolence was 5.7% in the Ambien CR group as compared to 2% in the placebo group.

**Rebound effects:** Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two 3-week placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of Ambien CR. On the second night, there was no worsening compared to baseline in the Ambien CR group.

In a 6-month placebo-controlled study in which Ambien CR was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Ambien CR 6.25 mg tablets are composed of two layers\* and are coated, pink, round, bi-convex, debossed with A~ on one side and supplied as:

<b>NDC Number</b>	<b>Size</b>
0024-5501-31	bottle of 100
0024-5501-10	carton of 30 unit dose

Ambien CR 12.5 mg tablets are composed of two layers\* and are coated, blue, round, bi-convex, debossed with A~ on one side and supplied as:

<b>NDC Number</b>	<b>Size</b>
0024-5521-31	bottle of 100
0024-5521-50	bottle of 500
0024-5521-10	carton of 30 unit dose

\*Layers are covered by the coating and are indistinguishable.  
Store between 15°-25° C (59°-77°F). Limited excursions permissible up to 30° C (86°F)

## 17 PATIENT COUNSELING INFORMATION

*See FDA-approved patient labeling (Medication Guide).*

Inform patients and their families about the benefits and risks of treatment with Ambien CR. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with Ambien CR and with each prescription refill. Review the Ambien CR Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that Ambien CR should be taken only as prescribed.

### CNS Depressant Effects and Next-Day Impairment

Tell patients that Ambien CR can cause next-day impairment even when used as prescribed, and that this risk is increased if dosing instructions are not carefully followed. Caution patients against driving and other activities requiring complete mental alertness the day after use. Inform patients that impairment can be present despite feeling fully awake.

### Severe Anaphylactic and Anaphylactoid Reactions

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

### Sleep-driving and Other Complex Behaviors

Instruct patients and their families that sedative hypnotics can cause abnormal thinking and behavior change, including “sleep driving” and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex). Tell patients to call you immediately if they develop any of these symptoms.

### Suicide

Tell patients to immediately report any suicidal thoughts.

Alcohol and Other Drugs

Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use Ambien CR if they drank alcohol that evening or before bed.

Tolerance, Abuse, and Dependence

Tell patients not to increase the dose of Ambien CR on their own, and to inform you if they believe the drug “does not work”.

Administration Instructions

Patients should be counseled to take Ambien CR right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Ambien CR tablets should not be taken with or immediately after a meal. Advise patients NOT to take Ambien CR if they drank alcohol that evening.

**MEDICATION GUIDE**  
**AMBIEN CR®** (ām' bē-ən see ahr)  
(zolpidem tartrate extended-release)  
**Tablets C-IV**

Read the Medication Guide that comes with AMBIEN CR before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

**What is the most important information I should know about AMBIEN CR?**

- **Do not take more AMBIEN CR than prescribed.**
- **Do not take AMBIEN CR unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take AMBIEN CR right before you get in bed, not sooner.**

**AMBIEN CR may cause serious side effects that you may not know are happening to you.**

**These side effects include:**

- sleepiness during the day
- not thinking clearly
- act strangely, confused, or upset
- “sleep-walking” or doing other activities when you are asleep like:
  - eating
  - talking
  - having sex
  - driving a car

**Call your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN CR.**

You should not drive a car or do things that require clear thinking the day after you take AMBIEN CR.

**Do not take AMBIEN CR if you:**

- drank alcohol that evening or before bed
- take other medicines that can make you sleepy. Taking AMBIEN CR with other drugs can cause side effects. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take AMBIEN CR with your other medicines.
- cannot get a full night’s sleep

**What is AMBIEN CR?**

AMBIEN CR is a sedative-hypnotic (sleep) medicine. AMBIEN CR is used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep

- waking up often during the night

It is not known if AMBIEN CR is safe and effective in children under the age of 18 years.

AMBIEN CR is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep AMBIEN CR in a safe place to prevent misuse and abuse. Selling or giving away AMBIEN CR may harm others, and is against the law. Tell your healthcare provider if you have ever abused or have been dependent on alcohol, prescription medicines or street drugs.

### **Who should not take AMBIEN CR?**

- Do not take AMBIEN CR if you are allergic to zolpidem or any other ingredients in AMBIEN CR. See the end of this Medication Guide for a complete list of ingredients in AMBIEN CR.
- Do not take AMBIEN CR if you have had an allergic reaction to drugs containing zolpidem, such as Ambien, Edluar, Zolpimist, or Intermezzo.

Symptoms of a serious allergic reaction to zolpidem can include:

- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

### **What should I tell my healthcare provider before taking AMBIEN CR?**

**AMBIEN CR may not be right for you. Before starting AMBIEN CR, tell your healthcare provider about all of your health conditions, including if you:**

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. It is not known if AMBIEN CR will harm your unborn baby.
- are breastfeeding or plan to breastfeed. AMBIEN CR can pass into your breast milk. It is not known if AMBIEN CR will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN CR.

**Tell your healthcare provider about all of the medicines you take**, including prescription and nonprescription medicines, vitamins and herbal supplements.

Medicines can interact with each other, sometimes causing serious side effects. **Do not take AMBIEN CR with other medicines that can make you sleepy unless your healthcare provider tells you to.**

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

### **How should I take AMBIEN CR?**

- See “What is the most important information I should know about AMBIEN CR?”

- Take AMBIEN CR exactly as prescribed. Only take 1 AMBIEN CR tablet a night if needed.
- Do not take AMBIEN CR if you drank alcohol that evening or before bed.
- You should not take AMBIEN CR with or right after a meal. AMBIEN CR may help you fall asleep faster if you take it on an empty stomach.
- Take AMBIEN CR Tablets whole. Do not break, crush, dissolve or chew AMBIEN CR tablets before swallowing. If you cannot swallow AMBIEN CR tablets whole, tell your healthcare provider. You may need a different medicine.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much AMBIEN CR or overdose, get emergency treatment.

### **What are the possible side effects of AMBIEN CR?**

**AMBIEN CR may cause serious side effects including:**

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See “What is the most important information I should know about AMBIEN CR?”)
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN CR.

**Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using AMBIEN CR.**

**The most common side effects of AMBIEN CR are:**

- headache
- sleepiness
- dizziness
- drowsiness the next day after you take AMBIEN CR

**After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as:**

- trouble sleeping
- nausea
- flushing
- lightheadedness
- uncontrolled crying
- vomiting
- stomach cramps
- panic attack

- nervousness
- stomach area pain

These are not all the side effects of AMBIEN CR. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

#### **How should I store AMBIEN CR?**

Store AMBIEN CR at room temperature, 59°F to 77°F (15°C to 25° C).

#### **Keep AMBIEN CR and all medicines out of reach of children.**

#### **General Information about the safe and effective use of AMBIEN CR**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use AMBIEN CR for a condition for which it was not prescribed. Do not share AMBIEN CR with other people, even if you think they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about AMBIEN CR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMBIEN CR that is written for healthcare professionals.

For more information, go to [www.ambiencr.com](http://www.ambiencr.com) or call 1-800-633-1610.

#### **What are the ingredients in AMBIEN CR?**

**Active Ingredient:** Zolpidem tartrate

#### **Inactive Ingredients:**

The 6.25 mg tablets contain: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide.

The 12.5 mg tablets contain: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807  
A SANOFI COMPANY

Month 2013

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019908Orig1s032s034**

**021774Orig1s013s015**

**MEDICAL REVIEW(S)**

**Clinical Review**  
**Required Safety Labeling Change: Ambien and Ambien CR**

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NDA:	19908, Ambien 21774, Ambien CR
Tracked Safety Issue	DARRTS #943
Reviewer:	Ronald Farkas, MD, PhD Clinical Team Leader, Division of Neurology Products DNP/OND/CDER

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## 1. Introduction

This is the third review by this reviewer addressing the risk of daytime impairment from residual zolpidem levels the day after as-labeled use of Ambien or Ambien CR. Previous reviews were filed in May 2012 and January 2013.

Required Safety Labeling Change Notification Letters were sent to Sanofi on January 9, 2013, and to the other sponsors of products containing zolpidem, requiring, in accord with section 505(o)(4), changes to prescribing information based on new safety information.

The letters to Sanofi noted the following:

1. Morning zolpidem blood levels after use of Ambien (zolpidem tartrate) tablets 10 mg or Ambien CR (zolpidem tartrate extended release) tablets 12.5 mg are high enough in some people, especially women, to impair driving. Excessively high zolpidem levels are more frequent after use of Ambien CR (zolpidem tartrate extended release) tablets.
2. Zolpidem blood levels in excess of 50 ng/mL, impair driving ability; the degree of impairment is similar to that observed with ethanol blood levels that are illegal for driving, and widely recognized as having the potential for an increase in the risk of traffic accidents, traffic-related injuries, and deaths.
3. Publications describing driving simulation or psychomotor test studies support that the impairment in driving ability is often not recognizable to the affected individual.

In addition to changes in safety warnings, the required changes included changing the recommended dose: for Ambien, from 10 mg to 5 mg in non-elderly women, and from 10 mg to either 5 or 10 mg for non-elderly men; and for Ambien CR, from 12.5 mg to 6.25 mg in non-elderly women, and from 12.5 mg to either 6.25 or 12.5 mg for non-elderly men.

Sanofi submitted on February 7, 2013 a rebuttal in response to the Required Safety Labeling Change Notification letters. The sponsor stated in the cover letter of their rebuttal that due to a lack of substantial evidence, they did not agree with the proposed changes in dosing. Sanofi did not state disagreement with the other required changes to labeling.

## 2. Rebuttal Documents

The following documents were submitted by the sponsor to both the Ambien and Ambien CR NDAs.

1. Summary of communications between the FDA and Sanofi regarding safety labeling changes for Ambien and Ambien CR (Attachment 1)

The Summary of Communications document briefly describes interactions between the Division and Sanofi, and does not provide any substantive rebuttal of the required labeling changes. While not presented as structured arguments, the sponsor indicates that in previous communications with the Division they argued that Ambien and Ambien CR are appropriately labeled, and that Sanofi has not identified any gender effects in clinical or postmarketing data. Also, Sanofi previously argued that lower doses of zolpidem had not been shown to be effective.

2. Response to FDA's safety labeling change notification dated January 9, 2013: Ambien and Ambien CR (Attachment 2)

Discussed below

3. Clinical overview: zolpidem driving impairment (Section 2.5)

The sponsor searched for postmarketing reports of traffic accidents involving Ambien or Ambien CR. The sponsor identified 1 case in which zolpidem involvement was judged to be probable. The sponsor concludes that there is no evidence from this data for a relationship between zolpidem and traffic accidents. However, as discussed in the review of January 2013, spontaneous reports and individual events are not adequately systematic to characterize the type of adverse events of concern for zolpidem, and have been affected by confounding (e.g. stimulated reporting for traffic accidents) such that analysis of such reports is not meaningfully reassuring of safety for Ambien and Ambien CR.

4. Pharmacokinetics of zolpidem immediate release formulation: effect of gender (Appendix 2)

This document contains PK data previously reviewed by FDA.

5. Pharmacokinetics of zolpidem extended release formulation: effect of gender (Appendix 3)

This document contains PK data previously reviewed by FDA.

### 3. Summary of Sponsor Rebuttal Arguments

The executive summary of the sponsor's rebuttal is the following:

1. Currently recommended doses do not result in next-day impairment
  - a. Clinical studies from NDAs: Results of placebo controlled clinical studies confirm that zolpidem, when used as recommended at the dose of 10 mg (IR formulation) and 12.5 mg (CR formulation) in non-elderly adults does not result in next day impairment in insomnia patients as shown on DSST, a validated measure of impairment commonly used in evaluating hypnotics. Post-hoc analyses of these data for Ambien IR and CR on psychomotor performance (using DSST and driving simulation tests) did not demonstrate any gender effect at the currently recommended doses (10 mg for IR and 12.5 mg for CR).
  - b. Medical Literature: Published clinical studies, including one that was conducted in an all female insomnia patient group, that evaluated the effect of zolpidem IR 10 mg administered at bed time on driving impairment show that zolpidem when used as recommended does not significantly impair driving, the day after dosing.
2. Potential safety risks with FDA's Proposed Dosage: Lack of efficacy at the proposed 5 mg dose for Ambien IR and 6.25 mg for Ambien CR could also create safety risks for patients. Lack of efficacy may result in an increased potential of patients adding another dose, at the beginning of the night or worse, take additional tablets during the night. As seen in a driving study conducted in female insomnia patients, the likelihood of during the night administration of zolpidem may in fact increase the potential for next morning impairment.
3. Intermezzo data do not apply to Ambien IR and Ambien CR: Sanofi does not believe that findings from studies with another formulation of zolpidem- Intermezzo (zolpidem, Purdue Pharma) 1.75 mg and 3.5 mg, can be used to draw conclusions regarding Ambien IR and Ambien CR due the different indication, dosage and administration for Intermezzo – sublingual intake after middle of the night awakenings. The driving study in the Intermezzo USPI was conducted using the same dose (3.5 mg) in male and female healthy volunteers, whereas the recommended dose in male and female patients is

different (3.5 mg and 1.75 mg, sublingually, respectively). It is important to note that the study did not include measurement of plasma concentrations prior to or immediately after driving test. In addition to these shortcomings, the clinical significance, if any of the pharmacokinetic/pharmacodynamic data for Intermezzo is not known, especially in relation to Ambien IR or Ambien CR.

4. Substantial Evidence of Efficacy At The Proposed Doses Has Not Been Established: The proposed changes to dosage not only affect the drug's safety profile, but also its efficacy profile. Consistent with the requirements of FDCA §505(d)(5) and the implementing regulations (21 CFR §201.56) and as stated by the Agency, approval of an NDA must be based upon "substantial evidence" showing that "the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." Substantial evidence implies that adequate and well controlled investigations have been conducted. The efficacy of 10 mg Ambien IR and 12.5 mg Ambien CR versus placebo is well established in clinical trials in non-elderly adult males and female insomnia patients. The efficacy of 5 mg Ambien IR and 6.25 mg Ambien CR has not been established in clinical trials, in either non-elderly adult male or female insomnia patients.

## 4. Review of Rebuttal Arguments

### 4.1 Sponsor Position: 'Currently recommended doses do not result in next-day impairment'

The sponsor asserts that currently recommended doses do not result in next-day impairment, but fails to acknowledge or address that the new finding of risk of next-day impairment occurs in only some patients, and that analysis of mean population values is likely to be insensitive to impairment that occurs in only some patients. Negative findings in a study without adequate statistical power are not interpretable.

For Ambien, the sponsor cites results on the Digit Symbol Substitution Test (DSST) from studies LSH08 and LSH10, stating that no deleterious next-day effects were observed, including in women analyzed separately. However, even though they analyzed the data by gender, they did not provide any analysis that takes into consideration impairment that might occur in only a subset of patients. They also provide no other evidence supporting assay sensitivity, such as positive-control findings.

For Ambien CR, the sponsor cites results from three pharmacodynamic studies (PDY4054, PDY5035 [elderly] and PDY5036 [adult]) and two efficacy studies (EFC4529 and EFC4530), although they state that data from EFC4530 is not included in their rebuttal as the study was conducted in only the elderly.

For the pharmacodynamic studies, they state that there was no evidence of significant residual effects on psychomotor performance and cognitive function, whereas a significant deterioration was observed after administration of flurazepam 30 mg. However, they did not analyze residual effect by gender or exposure, even though there is a large difference in morning blood level by gender; for example, in study PDY5036, the average 8.5 hour blood levels was 60 ng/ml for women (N = 8) and 18 ng/ml for men (N = 10) and zolpidem blood levels ranged from 4 ng/ml (with one subject's blood level below detection) to 148 ng/ml. Note that given the small number of observations in this study, any negative finding for impairment by gender or relative to exposure would be underpowered and unconvincing of safety.

The sponsor similarly argues that findings were negative for next-day residual effects (DSST and Rey Auditory Verbal Learning Test (RAVLT)) in efficacy study 4529, even when analyzed by gender. However, this negative result is unconvincing: the sponsor presents no analysis of results by exposure, has no positive-control to assess assay sensitivity, and notes that findings were confounded by learning effects.

As discussed in the two previous reviews, FDA re-analyzed data from study PDY4054, a 10-way crossover PK/PD study of 8 doses/combinations of immediate-release and delayed-release zolpidem in which a larger number of observations were available correlating morning zolpidem blood levels to residual psychomotor and cognitive effects. FDA found that morning blood levels after the 12.5 mg dose are clearly impairing in patients at the higher end of zolpidem exposures.

The sponsor further argues in their executive summary that the following studies demonstrate that Ambien and Ambien CR, when used as recommended, do not significantly impair driving the day after dosing. This review does not agree, as follows:

- *Staner L, Ertle S, Boeijinga P, Rinaudo G, Arnal M-A, Muzet A and Luthringer R. Nextday residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring. Psychopharmacology (2005) 181: 790-798.*

This study enrolled 9 men and 14 women, and examined the effects of zolpidem 10 mg, between 9 and 11 hours after dosing.

- *Vermeeren A, O'Hanlon JF, Declerck AC, and Kho L. Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation and placebo. Acta Therapeutica 1995 21(1):47-64*

This study enrolled 17 women, and examined the effects of zolpidem 10 mg, 10- to 11 hours after dosing.

- *Berthelon C, Bocca ML, Denise P, Pottier A. Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation? J Psychopharmacol 2003 17(3):324–331*

This study enrolled 4 men and 6 women, and testing began 10 hours after dosing zolpidem 10 mg.

- *Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effects of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. Psychopharmacology 1999 143(4):373-379*

This study enrolled 9 men and 7 women, and testing began in the earliest group (N = 8, 4 men and 4 women) 10 hours after dosing.

Reviewer discussion: The above 4 studies were small, and underpowered to detect impairment in the minority of patients with high morning blood levels. There was also lack of positive controls to confirm assay sensitivity. Negative findings are therefore not reassuring of safety.

- *Partinen M, Hirvonen K, Hublin C, Halavaara M, Hiltunen H. Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. Sleep Medicine (2003) 4:553–561*

This study enrolled 18 women (mean age 50), with driving simulator testing 5.5 hours after zolpidem 10 mg. The primary endpoint, Mean Time to Collision, did not differ between zolpidem and placebo, but the authors noted that inter-individual differences in performance were substantial, and the total number of off-road accidents after zolpidem was 6, compared to one accident both at baseline and after placebo. The authors also noted that inter-individual differences contributed to the lack of overall positive findings for the mean comparison. The author's final conclusion is that some patients are especially susceptible to residual effects of zolpidem, and carry a substantially increased risk of traffic accidents in real life. Also of note, a secondary outcome, lane position deviation, was positive for zolpidem compared to both placebo and temazepam, suggesting impairment based on the overall mean, not just a subset of patients. Mean zolpidem blood levels 5.5 hours after a 10 mg dose are about 40 ng/ml, and these levels were associated with impairment on lane position deviation. This review therefore concludes that this study supports the required safety

labeling changes, and does not support the sponsor's rebuttal arguments.

The sponsor cites additional reports, including on-the-road driving tests, epidemiological studies of sedative hypnotics, and motor vehicle accidents, and concludes that these studies are not sufficient to demonstrate an increased risk of next-day driving impairment following labeled use of Ambien IR or CR.

- *Verster JC and Roth T (2012) Gender differences in highway driving performance after administration of sleep medication: a review of the literature. Traffic Injury Prevention 13:286-292.*

This paper presented the individual subject SDLP values for men and women tested 4 hours after 10 mg zolpidem. Zolpidem levels in women 4 hours after 10 mg zolpidem are about 70 ng/ml. About 2/3 of the women at the 4 hour time point were impaired (increase in SDLP  $\geq$  3), and about 1/3 were severely impaired (increase in SDLP of about 12- to 14). This review finds, therefore, that this study supports that blood levels of 70 ng/ml or higher that commonly occur 8 hours after Ambien 10 mg or Ambien CR 12.5 mg are impairing.

- *Verster JC, Roth T (2011) Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. Psychopharmacology (Berl). 2012 March; 220(2): 293–301*

This paper specifically included zolpidem's affect on ability of drivers to predict their own driving impairment. The sponsor states "this article compares subjective vs. objective driving quality this is not directly applicable to Ambien [sic]" While not clearly stated, the sponsor appears to argue that the data on the ability of drivers to predict their own driving impairment after zolpidem is not applicable to Ambien or Ambien CR because the interval between dosing and testing was shorter than recommended in labeling. However, the sponsor provides no substantive argument to support why that makes the findings not relevant to Ambien or Ambien CR. Morning blood levels in this study overlap those found in patients after use of Ambien and Ambien CR as labeled, and testing was conducted in the morning, similar to actual clinical use. This review therefore concludes that study findings are applicable to the safety evaluation of Ambien and Ambien CR.

- *Mattila MJ, Mattila-Evenden ME (1997) Effects of alcohol and hypnosedative drugs on digit-symbol substitution: comparison of two different computerized tests. J Psychopharmacology 11:313-317*

The sponsor notes that a 15 mg dose of zolpidem was used, and patients were tested at 1, 3.5, and 5 hours after intake. The sponsor further argues that because experimental conditions differed from as-labeled use, findings are not relevant to understanding the effects of Ambien and Ambien CR. However, the sponsor provides no substantive argument why data on impairment from blood levels of zolpidem that are the same as the levels in many patients after use of Ambien and Ambien CR are not relevant to impairment from Ambien and Ambien CR. This review concludes, however, that studies of zolpidem at the same blood levels as occur after as-labeled use are relevant for evaluating the safety of Ambien and Ambien CR.

- *Publications supporting an association of sedative-hypnotic drugs and risk of traffic accidents*

The sponsor argues that publications that do not directly address zolpidem, and that conclude there is an association between certain sedative-hypnotic drugs and risk of traffic accidents, are not relevant to the safety of zolpidem (e.g. Barbone et al., 1998). This review concludes that class-effects of sedative-hypnotics are informative of the safety of other sedative-hypnotics, including zolpidem.

- *Epidemiological studies:*

*Gibson JE, Rubbard RB, Smith CFP, Tata LJ, Britton JR, Forgarty AW. Use of self controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. Am J Epidemiology 2009; 169: 761-768.*

The sponsor argues that this publication demonstrates that use of zolpidem as labeled is not associated with an increased risk of motor vehicle accidents. However, the study found an increased risk of traffic accidents at time points >4 weeks of use, a time period that is consistent with as-labeled use for both Ambien and Ambien CR.

*Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Morland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. Sleep Med 2008;9(8):818-822.*

The sponsor argues that the finding of an association between zolpidem and increased risk of traffic accidents is “highly confounded,” but presents no evidence supporting this assertion. The sponsor further notes that there are sources of confounding in epidemiological studies in general, but provides no evidence that these sources of

confounding invalidate the results of this study. The sponsor suggests that the finding of a numerically greater increase in risk in men versus women is meaningful, but the increase in risk is essentially the same for men and women, and provides no evidence that the study findings are invalid.

*Orriols L, Philip P, Moore N et al. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clin Pharmacol Ther 2011;89(4):595-601.*

The sponsor states that this study reported no increase in the risk of traffic accidents in patients who had normal zolpidem exposure, and an increase in risk in patients who had high zolpidem exposure due to use of more than the recommended dose. This review finds that this study supports FDA concerns, as high exposures occur in some patients with as-labeled use of Ambien and Ambien CR that are similar to the average levels from use of more than the recommended zolpidem dose, e.g. double the recommended zolpidem dose; these higher exposures are associated with road traffic accidents.

*Yang YH, Lai JN, Lee CH, Wang JD, Chen PC. Increased risk of hospitalization related to motor vehicle accidents among people taking zolpidem: case-crossover study. J Epidemiol 2011;21(1):37-43.*

The sponsor notes that there are sources of confounding in epidemiological studies, but provides no evidence that these sources of confounding invalidate the results of this study. The sponsor notes that the adjusted odds ratio for motor vehicle accidents for men was greater than for women, but provides no evidence that differences between men and women unrelated to zolpidem, like amount of time spent driving, do not account for this difference, and provides no substantive argument that the difference in risk between men and women meaningfully weakens study findings.

#### **4.2 Sponsor position: 'Potential safety risks with FDA's Proposed Dosage'**

The sponsor asserts that Ambien 5 mg and Ambien CR 6.25 mg are ineffective, and that patients potentially will take additional doses during the night, resulting in higher residual morning blood levels from lower doses than from higher doses, and greater risk of driving impairment from lower doses than from higher doses. However, the sponsor provides no evidence supporting this assertion.

As discussed below, ample evidence supports the efficacy of the FDA-required lower recommended doses, particularly on the first few nights of treatment. The magnitude of risk the sponsor speculates to exist is unknown, but seemingly

small, as it depends on the *fraction* of patients that obtain a *fraction* less efficacy from the lower versus higher dose over a *small* number of days before switching to the higher dose if needed (and as specifically directed in revised labeling), and on the *fraction* of those patients that consequent to the *fractionally* lower efficacy take an additional dose in the middle of the night, and the *fraction* of those patients that drive the next day despite the clear warnings in labeling that such use is dangerous. The sponsor speculates that the harm from this clearly labeled and seemingly small risk outweighs the risk of harm from the new, well documented, safety risk identified by FDA. Current recommended dosing is considered by patients and prescribers to be safe, yet in some patients leads to *extremely high* next-day zolpidem blood levels, higher, in fact, than the average blood levels found to be effective for inducing sleep: zolpidem blood levels higher than 50 ng/ml, and in some patients *several fold higher*, occur in approximately 15% of women and 3% of men 8 hours after zolpidem IR 10 mg, and in approximately 33% of women and 25% of men 8 hours after zolpidem MR 12.5 mg, with these high zolpidem levels having been demonstrated in multiple driving and laboratory studies to be capable of impairing driving abilities to a degree expected to increase the risk of motor vehicle accidents.

Furthermore, immediate-release zolpidem is considered safe despite a risk of middle-of-the-night re-dosing that, with *current* labeling, is essentially identical to the one cited by the sponsor. Sleep-maintenance insomnia is highly prevalent in the patients with sleep-onset insomnia who take immediate-release zolpidem. Immediate-release zolpidem has not been shown to be effective for sleep maintenance at *any* dose, and a large proportion of patients using immediate-release zolpidem experiences middle-of-the-night insomnia. These patients are at essentially the same risk of middle-of-the-night re-dosing as patients would be under the FDA-required labeling changes. While FDA recognizes that re-dosing in the middle-of-the-night occurs with use of immediate-release zolpidem and presents a safety risk, the benefit/risk profile of the immediate-release products in the context of middle-of-the-night dosing is essentially unchanged by the FDA-required labeling changes.

#### **4.3 Sponsor position: 'Intermezzo data do not apply to Ambien IR and Ambien CR'**

The sponsor argues that because of differences between Intermezzo and Ambien and Ambien CR, data from Intermezzo can not be applied to the safety of Ambien and Ambien CR. However, beyond listing differences between the products, the sponsor provides no substantive argument as to why, with appropriate consideration of such differences, data from Intermezzo provides no understanding of the safety of Ambien and Ambien CR. There seems to be no plausible explanation as to why similar residual morning blood levels of zolpidem would not cause similar degrees of driving impairment, despite the types of differences in experimental conditions listed by the sponsor.

The sponsor further argues that because blood zolpidem levels were not measured in driving studies of Intermezzo, the data is not useful for evaluating the safety of Ambien and Ambien CR. However, this review concludes that the pharmacokinetics of zolpidem is well enough established from other studies to interpret the Intermezzo driving study.

The sponsor argues that studies of zolpidem given by sublingual tablet are qualitatively different from, and have no bearing on Ambien and Ambien CR because of the difference in dosage form, yet provide no evidence to support this contention.

The sponsor argues that the simple fact that Intermezzo is approved for middle-of-the-night insomnia and that Ambien and Ambien CR are approved for use at the beginning of the night that safety findings from Intermezzo have no applicability to Ambien and Ambien CR. This review disagrees, as the specific circumstances of the study (e.g. dose, time of administration) are the only factors that affect information gained from the study, not the indication of the drug *per se*.

The sponsor argues, in the context of Intermezzo data, that functional impairment from zolpidem has not been shown to have clinical significance for driving. The sponsor does not, however, present any argument about degree of functional impairment, or degree of crash risk. As discussed in the previous two reviews, FDA concluded that the degree of functional impairment from Ambien and Ambien CR is likely to increase the risk of motor vehicle accidents.

The sponsor argues, in the context of Intermezzo, that studies of zolpidem in patients without insomnia can not be applied to Ambien and Ambien CR, yet provides no evidence to support this contention.

Finally, this review notes that the Intermezzo data is only one component of the overall data supporting the FDA action.

#### ***4.4 Sponsor Position: 'Substantial Evidence of Efficacy At The Proposed Doses Has Not Been Established'***

The sponsor argues that the laws and regulations governing FDA preclude recommending a dose of a drug that is effective for a patient subgroup or circumstance unless there is evidence equivalent to that required for approval supporting that specific dose. The sponsor's position is a misinterpretation of FDA laws and regulations; once a drug is found to be safe and effective, dosing recommendations for specific subgroups, like women, or recommendations for specific circumstances, like initial dosing, are not required to be supported by separate adequate and well-controlled investigations. Furthermore, as discussed in more detail in the previous review of January 2013, the lower doses of Ambien and Ambien CR are supported by adequate and well-controlled trials. there is

ample evidence of efficacy to support recommending the 5 mg dose for adults in the clinical situations described in the revised labeling: i) study LSH02 was positive for 5 mg zolpidem, with numerical superiority of the 2.5 mg dose; ii) study LSH10 was positive on night 2 for the 5 mg dose, and at day 7 the effect size of the 5 mg dose, 19 minutes, was essentially the same as the effect size for the 20 mg dose, 21 minutes; iii) study 4054 was positive for sleep latency at a time point in which zolpidem delivery from the 7.5 mg modified-release formulation approximated the zolpidem exposure from 5 mg zolpidem; iv) studies LSH10 (zolpidem immediate-release) and study 4530 (Ambien CR) were positive in elderly patients at the doses that would be recommended for adults under the required labeling changes, and after appropriate consideration by FDA of differences between elderly and adult insomnia patients, we conclude these studies in elderly patients provide strong evidence supporting the required labeling changes.

Furthermore, highly robust efficacy data from outside your development programs, such as the finding for Intermezzo of efficacy of zolpidem 1.75 mg for middle-of-the-night insomnia in women, and 3.5 mg for men, provides additional evidence of the pharmacodynamic activity of *very low* doses of zolpidem for inducing sleep in patients with insomnia, supporting the FDA-required labeling changes for Ambien and Ambien CR.

## 5. Conclusions

This review concludes that the sponsor's rebuttal is not persuasive, and that the FDA-required changes to labeling are necessary for the safety of Ambien and Ambien CR.

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RONALD H FARKAS  
03/15/2013

## Review and Evaluation of Clinical Data

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<b>NDA:</b>	<b>19908, Ambien 21774, Ambien CR</b>
<b>Sponsor:</b>	<b>Sanofi</b>
<b>Material Submitted:</b>	<b>Supplement 32 (Ambien) Supplement 13 (Ambien CR)</b>
<b>Correspondence Date:</b>	<b>6/12/2012</b>
<b>Reviewer:</b>	<b>Ronald Farkas, MD, PhD</b>

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On June 12, 2012 Sanofi submitted Changes Being Effected supplements to the Ambien and Ambien CR NDA's for the addition of "lower respiratory infection" [under 'frequent'] and "respiratory depression" [under 'rare'] in the **ADVERSE REACTIONS, Adverse event incidence across the entire preapproval database, Respiratory system** section of Ambien and Ambien CR prescribing information.

The sponsor states that following the publication of Joya et al (Joya FL et al., 2009, *Meta-analysis of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem*, J Clin Sleep Med 5(4):377-83), they reviewed all available safety data on zolpidem regarding infections. The sponsor also reviewed all available safety data on respiratory depression.

### Lower Respiratory Infection

The sponsor reports that in pre-approval studies influenza and lower respiratory tract infection occurred with higher frequency in the zolpidem CR group compared to placebo.

*Reviewer: I agree. Influenza and/or influenza-like illness are included in the table of common adverse events in both labels.*

The sponsor states that there were 80 postmarketing cases of infection, 56 of which were serious. Most cases were confounded by underlying disease or did not have enough information to determine a causal role for zolpidem

*Reviewer: I agree.*

The sponsor notes that Joya et al studied US FDA files combined with published studies of zolpidem. The relative risk for infection with zolpidem was 1.99 (95% CI 1.21-3.26). The sponsor expresses concern about bias inherent in meta-analysis, but considers the findings as potentially real.

*Reviewer: I agree*

*Reviewer conclusions:*

*The additional data and analysis in this submission is consistent with previous FDA safety findings, and does not reveal evidence that the risk of lower respiratory infection is higher than previously appreciated. I agree with the proposed labeling change.*

### **Respiratory Depression**

The sponsor reports that respiratory depression was not reported with an incidence of at least 1% in zolpidem IR studies, and no cases were identified in zolpidem CR trials. One serious case in a clinical trial of apnea after 20 mg zolpidem IR in a 28-year old patient was identified.

In postmarketing data, 85 serious, non-overdose cases of respiratory depression were reported. Most cases were associated with underlying disease or concomitant respiratory depressant medication. In 3 cases zolpidem was considered as the probable cause of worsened symptoms consistent with obstructive sleep apnea. The sponsor concludes that the causal role of zolpidem in respiratory depression seems possible.

The sponsor states that no additional case report or published safety study of respiratory depression with zolpidem was identified in the literature.

#### *Reviewer conclusions*

*Current zolpidem labeling includes a section in WARNINGS AND PRECAUTIONS describing studies conducted to determine the effect of zolpidem on respiratory depression in patients with chronic obstructive pulmonary disease and in patients with sleep apnea. Zolpidem had effects consistent with the term 'respiratory depression' that the sponsor proposes to add to the ADVERSE REACTIONS section of labeling. Rare cases of respiratory depression were identified in clinical trials. The postmarketing cases do not reveal that the risk of respiratory depression is higher than previously appreciated and represented in other sections of labeling. I agree with the proposed labeling change.*

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RONALD H FARKAS  
02/22/2013

## Clinical Review

### Required Safety Labeling Change: Ambien and Ambien CR

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<b>NDA:</b>	<b>19908, Ambien 21774, Ambien CR</b>
<b>Tracked Safety Issue</b>	<b>DARRTS #943</b>
<b>Reviewer:</b>	<b>Ronald Farkas, MD, PhD Clinical Team Leader, Division of Neurology Products DNP/OND/CDER</b>

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## 1. Introduction

This is the second of two reviews by this reviewer describing evidence that zolpidem blood levels the morning after as-labeled use of Ambien or Ambien CR remain high enough in some patients, mainly but not exclusively women, to impair next-morning driving ability to a degree that presents a safety risk both to individuals and the public. This review focuses on data generated by Sanofi; additional key evidence generated by other sponsors that supports the conclusions reached in this review is contained in the review filed in May 2012.

This review also describes interactions between the Division of Neurology Products (DNP) and the sponsor, Sanofi, regarding labeling changes to mitigate risk of next-day residual effects of zolpidem. The sponsor accepted some safety-related labeling changes proposed by DNP, but rejected recommending a lower dose for women, and a lower range of doses for men, arguing that the changes are not necessary for safety, and that there is inadequate evidence supporting the efficacy in adults of doses lower than those currently recommended (10 mg for Ambien and 12.5 mg for Ambien CR). This review presents the DNP response to Sanofi's safety and efficacy arguments.

The main conclusions of this review are as follows:

- Morning zolpidem blood levels after use of Ambien 10 mg or Ambien CR 12.5 mg are high enough in some people, especially women, to impair driving to a degree that poses a high risk to patients and the community. These high zolpidem levels are more frequent after use of Ambien CR. Zolpidem levels from Ambien and Ambien CR regularly exceed 50 ng/mL the morning after dosing, particularly in women (*Section 2*).

- Zolpidem levels of about 50 ng/mL and higher<sup>1</sup> impair some aspects of driving ability to a degree similar to, or greater than, impairment from blood ethanol levels that increase the risk of traffic accidents and related injuries and deaths several-fold, and that are illegal for driving. The effect of these blood levels of zolpidem on driving ability is ‘new safety information’ under the provisions of Section 505(o)(4) of the FDCA. (*Section 3*).
- The impairment in driving ability from these levels of zolpidem is often not recognizable to the affected individual. Changes to labeling limited to warnings are not adequate to address the safety risk from high exposure to zolpidem, and lower recommended doses, particularly for women, are necessary for the benefits of Ambien and Ambien CR to exceed risks in patients that drive. (*Section 4*).
- Adequate evidence supports recommending 5 mg for Ambien and 6.25 mg for Ambien CR for treatment of insomnia in both adult men and women, with dosing increased (to 10 mg or 12.5 mg, respectively) if necessary for efficacy (*Section 5*).

## 2. Morning Zolpidem Blood Levels

In August 2011, DNP sent an information request to Sanofi for data regarding gender differences in zolpidem levels, including differences in next-morning blood levels. Sanofi submitted the requested information for Ambien CR in October 2011 and January 2012, and for Ambien in February 2012.

High morning zolpidem blood levels<sup>2</sup> from Ambien and Ambien CR are illustrated by the following studies conducted by Sanofi<sup>3</sup>:

- Ambien, study 4054: In a PK/PD study of 16 adult women and 20 adult men the average zolpidem blood level 8.5 hours after dosing of 10 mg Ambien<sup>4</sup> was 38 ng/mL in women and 17 ng/mL in men. In women, 5 of 16 subjects had a blood level  $\geq 50$  ng/mL, with the highest level 92 ng/mL. Only 1 of 17 men had a blood level  $\geq 50$  ng/mL, with that single subject’s level 61 ng/mL.
- Ambien CR: Mean blood level 8.5 hours after dosing Ambien CR 12.5 mg was 49 ng/mL in women (N = 22) and 21 ng/mL in men (N = 29) in phase 1 studies.<sup>5</sup> Of note, in the phase 3 efficacy study for Ambien CR

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<sup>1</sup> It should be emphasized that as zolpidem blood levels increase above 50 ng/mL, essentially no doubt remains that impairment as measured by these specific pharmacodynamic tests is at least as severe as from ethanol at the legal limit for driving.

<sup>2</sup> For these purposes, levels greater than 50 ng/ml and that impair driving performance will be considered high.

<sup>3</sup> The main analysis of zolpidem blood levels is contained in the earlier review filed in May 2012.

<sup>4</sup> The European version, Stilnox, was used

<sup>5</sup> combined studies BDR5477, BDR5478, and PDY5035, per sponsor’s calculations in document *response-26-sept-2011*

(EFC4529), which may be more representative of exposure in a clinical setting, the sponsor reports mean morning blood levels that were far higher, 43 ng/mL in men (N=34), and 70 ng/mL in women (N=53), 9 hours after dosing. The average blood level in women is 2.6-fold higher than in men in the interval between 6 and 12 hours after dosing.

In the dataset of zolpidem extended-release blood levels assembled by Sanofi in the October 2011 submission, after dosing of 6.25 mg Ambien CR in 23 women and 47 men, the highest 8-hour zolpidem level was about 95 ng/mL for both men and women. For the 6.25 mg dose in 23 elderly women and 47 elderly men, the highest zolpidem levels were 76 ng/mL in women and 67 ng/mL in men. At 12 hours after use of zolpidem extended release in a dataset of 36 women and 36 men, the highest blood levels were 65 ng/mL and 42 ng/mL, respectively.

Figure 1 shows zolpidem blood levels for about 100 individual adult men and women after a dose of 12.5 mg Ambien CR. The red line is the average blood level. Morning blood levels in some patients are strikingly high, at or above the average C<sub>max</sub> of the drug. Even if the dose was reduced by half in all patients, roughly 5% would have morning zolpidem levels  $\geq$  50 ng/mL.

**Figure 1: Zolpidem Blood Levels after Ambien CR 12.5 mg**

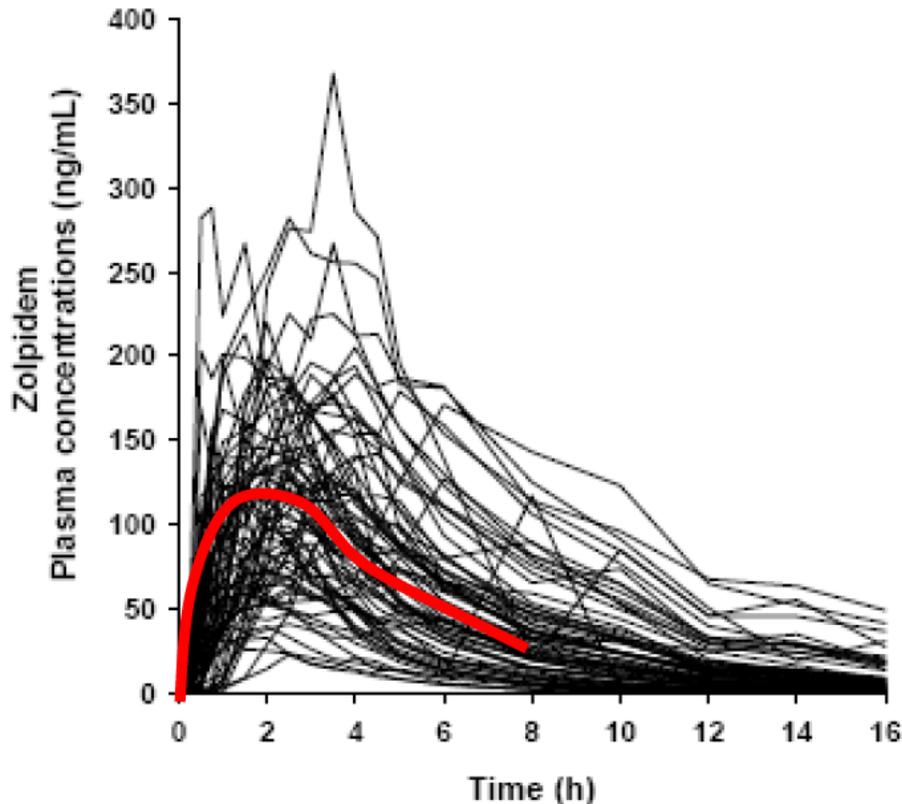


Figure from Sanofi Study BDR5478

### **3. Zolpidem and Driving Impairment**

#### **Study 4054**

As described in more detail in the review filed in May 2012, in the drug development program for Ambien CR, a 10-way crossover PK/PD study was conducted with 8 doses/combinations of immediate-release and delayed-release zolpidem (study 4054, N=36, 16 women, 20 men). Subjects were given drug before bed, and tested after awakening in the morning. Blood samples were collected at 8.5 hours post-dose. One PD endpoint was the Digit Symbol Substitution Test (DSST), a test of psychomotor performance that requires subjects to match symbols with corresponding digits. Performance on the test is affected by skills relevant for driving: attention, perceptual speed, motor speed, visual scanning, and memory. Another PD endpoint was mean reaction time (MRT), a measure with clear relevance to identifying and avoiding road hazards. The data was analyzed by Dr. Joo-Yeon Lee and Dr. Yaning Wang in the Division of Pharmacometrics (CDER/OTS/OCP). Deficits of a severity roughly corresponding to those from alcohol at the legal limit for driving occurred for

MRT<sup>6</sup> at about 55 ng/mL and for DSST at about 65 ng/mL,<sup>7</sup> with an apparent rapid exponential increase in impairment for both at higher zolpidem levels.

This review presents additional analysis of this study. As discussed below, Ambien CR did *not* show statistically positive results as originally analyzed prior to approval; however, re-analysis of the *combined* data from the several zolpidem formulations tested indicates that the high morning blood levels that occur in some patients after use of Ambien CR *are* impairing. Eight psychomotor tests were conducted the morning after dosing of the different zolpidem formulations. Three of the zolpidem formulations, F, G, and H (see Figure 2 legend for doses) induced statistically significant impairment of psychometric and cognitive function. Table 1 shows the psychomotor tests that were statistically positive 8 or 9 hours after dosing of the different formulations, including Ambien 10 mg (Stilnox is the European version of Ambien), and Ambien CR (formulation E).

**Table 1: Psychomotor test and zolpidem formulations**

Table (11.5.1.2.2) 3 – Summary of the statistical analyses of the psychomotor test results at 8 hours and 9 hours post dose

	A	B	C	D	E	F	G	H	Stilnox
CFE (Hz)	-	-	-	-	-	-	-	-	-
CTTd (pixels)	-	-	+ at 8h	-	-	+ at 8h + at 9h	-	+ at 9h	-
CTTt (ms)	-	-	+ at 8h	+ at 9h	-	+ at 8h	+ at 8h	+ at 9h	+ at 9h
DSST No. completed	-	-	+ at 8h	-	-	+ at 9h	+ at 9h	-	-
CRT – Motor reaction time (ms)	-	-	-	-	-	+ at 8h	-	+ at 8h	-
CRT – Recognition reaction time (ms)	-	+ at 9h	-	+ at 8h	-	-	-	-	-
WRd* (n)	-	-	-	-	-	+ at 8h	+ at 8h	+ at 8h	-
WRi* (n)	-	-	-	-	-	-	-	+ at 8h	-

\* Not performed 9 hours post-dose

+ : test statistically different from placebo

- : test not statistically different from placebo

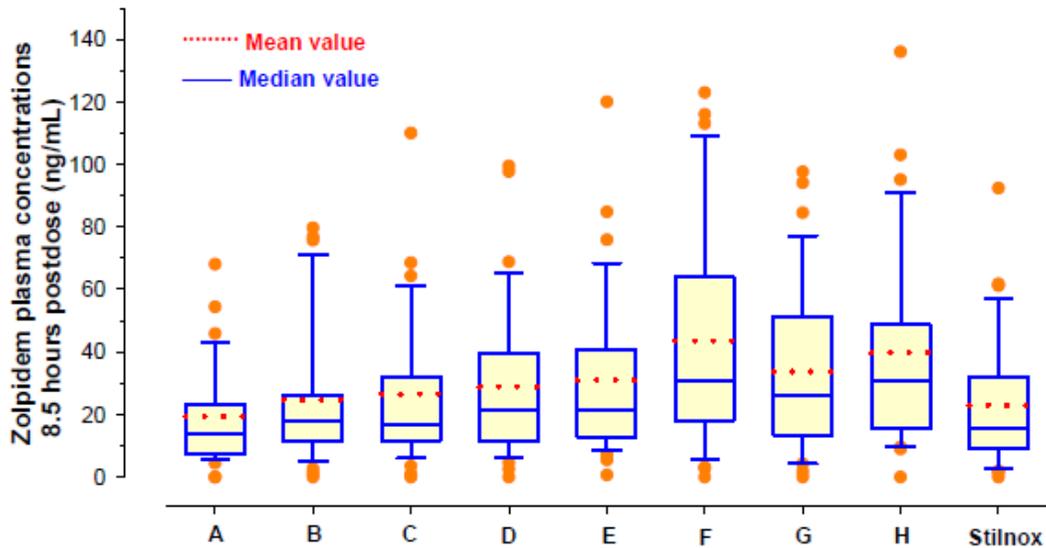
CFE, critical flicker fusion; CTTd, compensatory tracking task; DSST, digit symbol substitution test; CRT, choice reaction time; WRd, delayed word recall; WRi, immediate word recall

Figure 2 shows zolpidem *blood levels* 8.5 hours after dosing of the zolpidem formulations. The morning after taking Ambien CR (E) some patients have zolpidem blood levels essentially as high as the highest blood levels in formulation F, G, and H, the formulations causing statistically significant impairment. Given the known dose/response relationship of zolpidem, if *average* zolpidem blood levels in a cohort are impairing, the *highest* blood levels in that cohort seemingly must be impairing (and in fact are almost certainly more impairing than the average blood level in that cohort). This review therefore concludes that the same high zolpidem blood levels that occur in some patients after use of Ambien or Ambien CR similarly would be impairing.

<sup>6</sup> Tzambazis K and Stough C (2000) *Alcohol impairs speed of information processing and simple and choice reaction time and differentially impairs higher-order cognitive abilities.* Alcohol and Alcoholism 35:197-201.

<sup>7</sup> Brumback T et al (2007) *Effects of alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers.* Drug and Alcohol Dependence 91:10-17

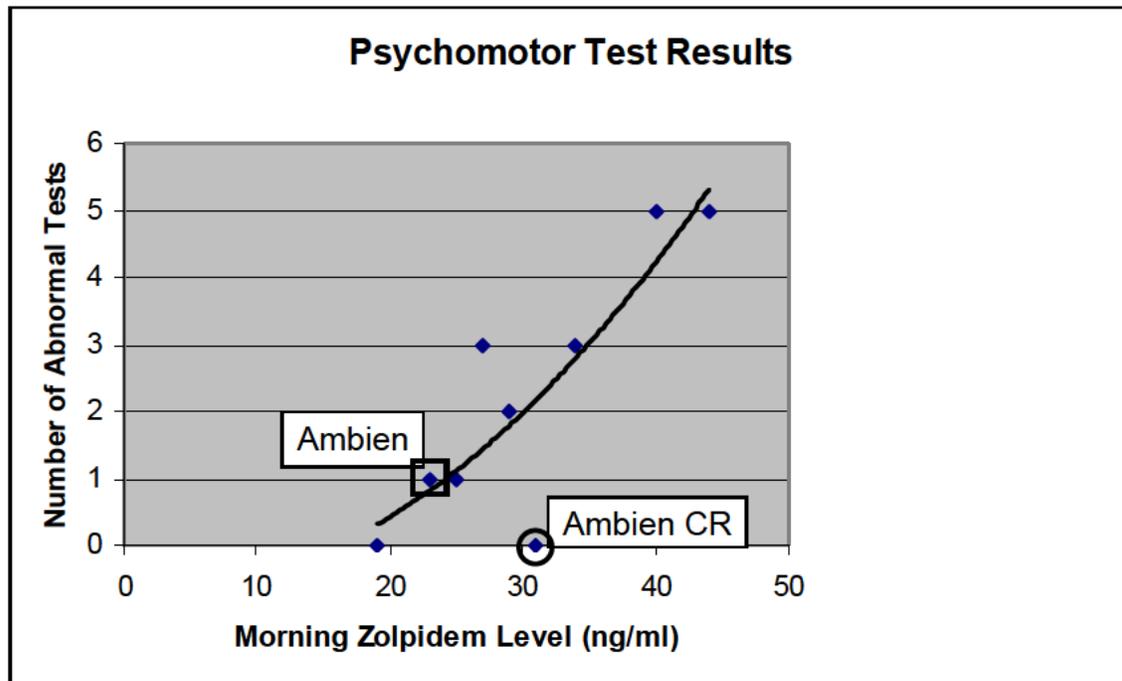
**Figure 2: Zolpidem blood levels for formulations**



From figure 11.4.1.1, page 40/84 of study 4054 report: *Distribution of plasma concentrations of zolpidem obtained 8.5 hours after a single oral administration, presented by formulation. Total dose: A, 7.5 mg; B, 10 mg; C, 12.5 mg; D, 10 mg; E, 12.5 mg (equivalent to Ambien CR); F, 15 mg; G, 12.5 mg; H, 15 mg; Stilnox, 10 mg (equivalent to Ambien)*

Figure 3 shows average zolpidem blood levels the morning after the different zolpidem formulations, plotted against the number of psychomotor tests (out of the total of 8) that showed statistically significant impairment. There is a clear association of impairment with increasing average morning zolpidem levels. While the observed Ambien CR data falls below the regression line, the true degree of impairment from the drug is likely more accurately estimated by the regression line, which is based on the combined data from the several tested formulations.

**Figure 3: Zolpidem Mean Blood Levels and Impairment**



Ambien 10 mg data point: square, Ambien CR 12.5 mg data point, circle

### Published Studies

Additional evidence that morning zolpidem levels in some patients are impairing is provided by published studies.

- Mattila et al<sup>8</sup> studied effects of zolpidem on psychomotor tests at several time-intervals after dosing of 15 mg. Ethanol was included as a study arm, allowing direct comparison of ethanol- and zolpidem-induced impairment. *While 15 mg is higher than the labeled dose, zolpidem blood levels were measured, allowing correlation of impairment with zolpidem levels that can occur with as-labeled use of the marketed products.* Zolpidem at an average blood level in the test group of about  $65 \pm 13$  ng/mL resulted in impairment similar to that from ethanol near the *per se* limit for driving. Zolpidem blood levels of 65 ng/mL or higher occur in a substantial subset of patients in the clinical population after use of Ambien 10 mg or Ambien CR 12.5 mg.
- Verster and Roth reported gender-specific results of an on-the-road driving test of zolpidem. The primary outcome was 'Standard Deviation of Lateral Position' (SDLP) a measure of how well a subject is able to maintain the vehicle in the driving lane. Such measures have high face-validity for clinically meaningful driving impairment. Zolpidem 10 mg was dosed 4 hours before driving. This is shorter than the labeled

<sup>8</sup> Mattila MJ et al. (1998) *Effects of Alcohol, Zolpidem, and Some Other Sedatives and Hypnotics on Human Performance and Memory.* Pharmacology Biochemistry and Behavior, 59:917-923.

7- to 8 hour interval before driving, and consequently subjects had much higher zolpidem blood levels than the *average* level expected from use as-directed. *Importantly, however, blood levels in many women 7- to 8 hours after as-labeled use of Ambien or Ambien CR are essentially the same as the average level in women in this study 4 hours after dosing.* Based on data from separate PK studies, average blood level in the women in this study (4 hours after 10 mg zolpidem) was likely about 70 ng/mL. The increase (worsening) in SDLP observed was about 7 cm, comparable to the effect of a BAC of 0.10%.

### **Additional Considerations**

Driving while sleepy is a major cause of motor vehicle accidents.<sup>9</sup> The primary pharmacodynamic action of zolpidem is to increase sleepiness. Blood levels of zolpidem that are effective for inducing sleep appear likely to increase the risk of motor vehicle accidents. Study LSH02 was a well-controlled trial of zolpidem immediate release in transient insomnia. The study examined doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 20 mg zolpidem, versus placebo, in 17 healthy males.<sup>10</sup> Statistically significant reduction in sleep latency versus placebo was demonstrated for doses as low as 5 mg, with numerical superiority of the 2.5 mg dose. While zolpidem blood levels were not measured in the study, average  $C_{max}$  would be expected to have been about 30 ng/mL after the 2.5 mg dose and 60 ng/mL after the 5 mg dose. Similarly, efficacy studies of Ambien CR demonstrated an effect on sleep maintenance through 6 hours after dosing, when the average blood zolpidem blood level was about 50- to 60 ng/mL. As noted in Section 3, a significant minority of patients taking Ambien an Ambien CR have zolpidem blood levels up to several-fold higher than levels shown to increase sleepiness.

While not a primary support for DNP's conclusions, epidemiological studies of both zolpidem and other sedative-hypnotics also suggest that the pharmacodynamic effects of this class of drugs are associated with an increased risk of motor vehicle accidents.<sup>11</sup>

In the United States, driving with a blood alcohol concentration (BAC) of 0.08% or higher is illegal *per se*, while in most European countries the *per-se* limit is 0.05%. In a review of the relationship between risk of fatal automobile crash and BAC the National Highway Traffic Safety Administration concluded that there is overwhelming evidence that BAC as low as 0.02% impairs driving-related skills.<sup>12</sup> The Long Beach/Fort Lauderdale relative risk study, a case-control study that

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<sup>9</sup> National Transportation Safety Board, 1999. Evaluation of U.S. Department of Transportation Efforts in the 1990s to Address Operator Fatigue. National Transportation Safety Board, Safety Report NTSB/SR 99/01, Washington, D.C.

<sup>10</sup> Merlotti L et al (1989) *The dose effects of zolpidem on the sleep of healthy normals.* J Clinical Psychopharmacology 9:9-15.

<sup>11</sup> See Appendix

<sup>12</sup> Zador et al., DOT HS 809 050 April 2000 *Relative risk of fatal crash involvement by BAC, age, and gender*

quantified the risk of *actual* fatal crash versus BAC, found, respectively, that a BAC of 0.02%, 0.035%, and 0.065%, roughly doubled, tripled, and increased 10-fold the risk of fatal single-vehicle crash (with a continued steep exponential increase in risk at higher BAC).<sup>13</sup>

Finally, while impaired next-day driving from zolpidem is the main impetus for the current dosing revision, high nighttime zolpidem levels are also a safety concern. Data submitted in the original NDA for Ambien show that common adverse events including confusion, dizziness, and amnesia begin to increase sharply with doses of zolpidem only 50% higher than the recommended 10 mg adult dose. At a dose of 20 mg, roughly 5- to 15% of patients experience these adverse events. Rare but more serious adverse events, like sleep-driving and other types of bizarre behavior, may be associated with blood levels only a few-fold higher than the average C<sub>max</sub> from the 10 mg dose.<sup>14</sup> Patients at the high end of the distribution of exposures from the 10 mg dose, who have exposure similar to that from these higher doses, may therefore be at similar high risk of adverse events.

### **Sponsor arguments, Safety**

The sponsor argued in a July 17, 2012 correspondence to the Division that there is *not* substantial evidence to support the clinical meaningfulness of the higher exposure to zolpidem in women versus men from Ambien or Ambien CR. The sponsor stated that a statistically significant difference in spontaneous adverse events between men and women was not found in their postmarketing database, and that the Division did not cite specific cases upon which the labeling change was based. The sponsor further appeared to argue that the relationship between exposure and the adverse effects precipitating the labeling change were a “theoretical assumption or possibility” that does not support a safety labeling change.

The Division considered the sponsor’s arguments, but did not agree based on the following. Significant differences in spontaneous adverse events between women and men, or single convincing individual adverse events, are rarely necessary to support the proposed safety labeling change if other adequate data is available. Spontaneous reports and individual events are not adequately systematic to characterize the type of adverse events of concern for zolpidem, and have been affected by confounding (e.g. stimulated reporting for traffic accidents) such that analysis of such reports is not meaningfully reassuring of safety for Ambien and Ambien CR.

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<sup>13</sup> Blomberg RD et al (2009) The Long Beach/Fort Lauderdale relative risk study. J Safety Res 40:285-292.

<sup>14</sup> Southworth et al (2006) Nonbenzodiazepine hypnotic use and cases of “sleep driving.” Ann. Int. Med 148(6):486-487.

The sponsor communicated on August 22, 2012 additional arguments that Ambien and Ambien CR dosing should not be changed due to safety concerns. The sponsor argued that *post-hoc* analysis of study 4529 (Ambien CR), LSH08 and LSH10 (Ambien) found no deleterious effects on the overall population as measured by DSST from the 12.5 mg Ambien CR and 10 mg Ambien doses, including when results were analyzed by gender. The Division finds this argument does not provide persuasive evidence for safety. The Division is concerned about unsafe zolpidem levels in patients *at the high end of the population distribution*, not average effects. While average effects of next-day psychomotor performance are currently represented in labeling, this is an insensitive approach to detecting adverse effects in patients at the high end of the distribution of exposures; similar to analysis of any other adverse event (e.g. hematologic or hepatic abnormality), an ‘outlier’ analysis is necessary to identify patients at increased risk. There is clear evidence from adverse events reports (a type of outlier analysis) from phase 3 studies of an increased risk of next-day somnolence from Ambien and Ambien CR. For example, in Ambien CR study LTE5407, zero of 351 placebo patients discontinued due to next-day somnolence, while 8 of 674 Ambien CR patients discontinued due to this adverse event. The table of common adverse events in Ambien CR labeling indicates a 15% incidence of somnolence associated with drug, vs. 2% for placebo, along with numerous similar adverse events more frequent in drug-treated patients, like psychomotor retardation, disorientation, disturbance in attention, etc. Similarly, for Ambien 10 mg, common adverse including drowsiness, lethargy, and drugged feeling were more common in drug- vs. placebo-treated patients.

In the August 22 communication to the Division, the sponsor also disagreed that epidemiological studies cited by the Division were sufficient to demonstrate an increased risk of next-day driving impairment in women following labeled use of Ambien.<sup>15</sup> The sponsor noted known limitations of such studies, including potential confounding by other drugs or alcohol, and the fact that the exact dose and timing are unknown in epidemiological studies. The Division first notes that the sponsor’s use of the word ‘sufficient’ appears to create a false dichotomy in the role of these studies in the Division’s overall safety conclusions; the Division interprets the epidemiological studies in the context of their known limitations, and in conjunction with the analysis provided above, concludes that the overall evidence supports the Division’s conclusions. The sponsor also objected that some of the epidemiological studies the Division cited in support of sedative-hypnotics increasing the risk of traffic accidents did not specifically assess risk from zolpidem. However, the Division disagrees with this concern, as studies supportive of risk from sedative hypnotics as a drug class are relevant to zolpidem, a member of that drug class. The sponsor specifically argued that Gibson et al<sup>16</sup> does not support an increased risk of traffic accident from

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<sup>15</sup> See Appendix

<sup>16</sup> Gibson JE et al. (2009) *Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes*. American Journal of Epidemiology 169:761-768.

zolpidem because short-term use (less than 4 weeks) was not associated with increased risk. The Division notes, however, that an increased risk was found for zolpidem after prolonged exposure. The sponsor argued that Orriols<sup>17</sup> et al only showed an increased risk of motor vehicle accidents with use of one tablet or more a day, not one pill or less, such that 'normal exposure' was not associated with increased risk. The Division notes, however, that it is primarily patients at the high end of exposure that are the main focus of safety concern, and the findings support the positive correlation between zolpidem exposure and risk of automobile accidents.

The sponsor also objected to the Division relying on Verster and Roth<sup>18</sup> and Mattila et al<sup>19</sup> because Verster and Roth studied driving 4 hours after dosing, and Mattila et al studies effects of a 15 mg dose of zolpidem, neither of which is a labeled use of zolpidem. However, as noted above, the Division used these studies to correlate impairment with estimated zolpidem blood levels, and did not rely on a simple comparison of one dose or use to another.

#### 4. Risk Mitigation

The sponsor argued that there are several cautionary statements directed at the prescriber and the patient in the current labeling for Ambien and Ambien CR that provide important information that both the prescriber and patient need to be aware of for the safe and effective use of these products. The Division concludes, however, that the current warnings are inadequate to provide for safe use of the products as currently dosed. The sponsor noted that current labeling recommends that the dose "be individualized." The Division concludes, however, that instructions encouraging individualized dosing do not adequately mitigate the safety risk from high zolpidem levels that arise from current dosing recommendations; simply put, initial treatment with too high a dose is unsafe.

Furthermore, evidence has increased in recent years that patients taking psychoactive medications like zolpidem can be impaired without feeling impaired, and even can feel subjectively improved when objectively impaired. There appears to be *no* evidence that safety concerns related to next-day residual drug levels are adequately addressed by instructing patients taking zolpidem to refrain from driving or other dangerous activities until they feel 'fully awake' or 'know

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<sup>17</sup> Orriols L et al (2011) *Benzodiazepine-Like Hypnotics and the Associated Risk of Road Traffic Accidents*. *Clinical Pharmacology and Therapeutics* 89:595-601.

<sup>18</sup> Verster JC, Roth T (2011) Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. *Psychopharmacology (Berl)*

<sup>19</sup> Mattila MJ, Mattila-Evenden ME (1997) Effects of alcohol and hypnotic drugs on digit-symbol substitution: comparison of two different computerized tests. *J Psychopharmacology* 11:313-317.

how the drug affects them.’ Concern might even be raised that such instructions promote *unsafe* drug use by conveying that driving is safe when drug levels are likely to be high so long as the patient ‘feels fully awake.’

Verster and Roth<sup>20</sup> tested the hypothesis that adverse drug effects such as reduced alertness may cause drivers to be unaware that their driving is impaired. They analyzed data from on-the-road driving tests using SDLP as the primary outcome. While their analysis revealed statistical correlations between patient perception and actual performance, they stress that the correlations are not adequately robust for patients to be able to rely reliably on the general advice that “patients should listen to their body, and not drive if they feel their driving is impaired.”

Mattila and Mattila-Evenden<sup>21</sup> examined performance on laboratory-based tests of psychomotor impairment after daytime dosing of alcohol and several sedative-hypnotics including zolpidem 15 mg. Patients were asked to self-rate their level of drowsiness, clumsiness, mental slowness, and overall performance. The study found that correlation of these subjective ratings to the object measures of performance was low or negligible.

## 5. Efficacy of Lower Doses of Ambien and Ambien CR

The sponsor argued against recommending a lower dose for Ambien and Ambien CR based on a lack of substantial evidence of effectiveness of the lower doses. However, DNP finds that when substantial evidence of effectiveness has been established for a drug such as Ambien or Ambien CR, *in both adult and elderly patients*, dosing recommendations for patient subgroups can be based on a variety of sources of both efficacy and safety data. For example, it is clearly not required that labeling for patients with hepatic impairment, or for drug-drug interactions, requires separate well-controlled efficacy studies. That said, DNP believes that persuasive efficacy data is available to support lower initial dosing recommendations for Ambien and Ambien CR in adults, with the option of higher dosing if needed for efficacy.

The studies listed below were positive for efficacy for the lower proposed dose of Ambien and Ambien CR, 5 mg and 6.25 mg respectively, in both older and younger adults. Note that the Ambien CR studies at 6.25 mg are also supportive of efficacy of Ambien at 5 mg for sleep latency, since Ambien CR is effective for *both* sleep latency (the indication for Ambien) and sleep maintenance.

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<sup>20</sup> Verster JC, Roth T (2011) Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. *Psychopharmacology (Berl)*

<sup>21</sup> Mattila MJ, Mattila-Evenden ME (1997) Effects of alcohol and hypnotic drugs on digit-symbol substitution: comparison of two different computerized tests. *J Psychopharmacology* 11:313-317.

#### Ambien (sleep latency)

- LSH02, 5 mg, acute insomnia in young men
- LSH11, 5 mg, acute insomnia in elderly men and women
- LSH10, 5 mg, chronic insomnia in adult men and women
- Study 4054,  $\approx$  5 mg in young adults, estimated from amount of zolpidem released from a 7.5 mg modified-release formulation in the first 30-minutes after dosing

#### Ambien CR (sleep latency and sleep maintenance)

- Study 4530, 6.25 mg in chronic insomnia in elderly men and women
- Study 4529, 12.5 mg, PK analysis shows zolpidem levels for adult women are about twice as high as for men, such that exposure from 6.25 is a reasonable initial dose for women

### **Sponsor arguments, efficacy**

The paragraphs below address arguments that efficacy findings from studies conducted in older adults do not provide information useful for making dosing recommendations in younger adults (particularly relevant for Ambien CR, for which study 4530 in elderly patients was the only phase 3 study conducted with the 6.25 mg dose):

#### *Age-related differences in zolpidem exposure*

- This review concludes that it is reasonable to base dosing recommendations on studies in elderly in part because inter-individual variability in zolpidem exposure in patients of the same or similar age is much larger than exposure differences in exposure due to age, and likely has a greater impact on safety and efficacy than age-related differences. In the typical PK study, zolpidem C<sub>max</sub> varies about 5-fold. For example, Ambien labeling describes a study in 45 healthy adults given the 10 mg dose, with C<sub>max</sub> ranging from 58 to 272 ng/mL. In larger populations that better capture the true degree of variation in the clinical population, a larger range for C<sub>max</sub> is found, about 10-fold or more (e.g. see figure of Ambien CR individual PK data in Section 2). Exposure to zolpidem several hours after dosing shows even higher inter-patient variability. For example, blood levels at 6 hours after dosing Ambien CR vary about 100-fold (0.8 ng/mL to 96 ng/mL, N = 70 adults).
- Also of note, because of the large range of zolpidem blood levels across individuals, at a dose that *on average* is effective, efficacy *predictably* will be lower in individuals at the low end of the exposure distribution. However, despite this it can be reasonable to recommend a specific dose for the overall population. Particularly in cases where labeling allows an increased dose if an initial lower dose is not effective (as does labeling proposed by the Division for Ambien and Ambien

CR), it would be inappropriate to recommend a higher dose that had an unfavorable safety profile for a significant proportion of patients.

- Zolpidem labeling indicates that exposure is about 50% higher in elderly patients. However, this value was from a single study enrolling 8 patients age 70- to 85 years. The effect of age on exposure appears to be both unpredictable and smaller, except at extreme age. In study IFR38, elderly patients 60-74 years (N=11, 5 males, 6 females) had a C<sub>max</sub> of 108 ng, *lower* than the C<sub>max</sub> reported in labeling for young adults in Ambien labeling. Similarly, the AUC(inf) in patients in study IFR38 was 715 ng·hr/mL, *lower* than the AUC reported in labeling for young adults, 740 ng·hr/mL. A large age-related increase in exposure does appear to occur at age extremes; for example, in study IFR34, which enrolled patients 81- to 95 years (N=9, 7 females, 2 males), C<sub>max</sub> was about 70% higher, and AUC was about 3-fold higher versus young adults.

*Age-related differences in insomnia between older and younger adults*

- While some baseline differences in insomnia exist between older and younger populations, these differences appear generally to be small. The incidence of insomnia is higher in older versus younger adults, but mostly because of other age-related conditions, not age *per se*.<sup>22</sup> Changes in sleep architecture between young adulthood and middle-age are far more dramatic than changes after age 35. Thus, on the basis of sleep characteristics, efficacy from studies in elderly are likely at least as useful for informing dosing in younger adults as data in middle-age patients would be for making dosing recommendations in younger adults.
- Inter-individual differences in the underlying condition of insomnia for which patients take Ambien or Ambien CR appear to be far larger than age-related differences. This is due in large part to the fact that these drugs are approved for 'insomnia', not a specific type or etiology of insomnia.
- Baseline insomnia symptoms were similar in studies of younger and older adults. In study 4529 baseline median total sleep time (TST) was 362 minutes in younger adults, with a range of 136- to 455 minutes, while in study 4530 in older adults, baseline median TST was 343 minutes, with a range of 122- to 436 minutes; inter-patient variability in each age group was clearly much greater (about 10-fold) than any age-related difference. Measures of insomnia specific to latency and maintenance showed similar patterns, with much larger inter-individual differences than differences potentially attributable to age. It should also be noted that differences due to gender appear to be larger than age-related differences; in study 4530, baseline WASO in the first and middle parts of the night was a median of about 70 minutes in men (N=86), but only about 54 minutes in women (N=117).

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<sup>22</sup> Ancoli-Israel (2009) *Sleep and its disorders in aging populations*. Sleep Med 10:S7-11.

The paragraphs below addresses arguments that efficacy findings from studies conducted in acute insomnia do not provide information useful for making dosing recommendations in chronic insomnia:

- The distinction between acute and chronic insomnia is not well-defined. Different classification schemes in current use differ in how subtypes of insomnia are defined. Thus, the insomnia model studied in healthy subjects was similar to ‘extrinsic sleep disorders’ that can be acute, subacute, or chronic.<sup>23</sup>
- There appears to be little to no evidence that efficacy of zolpidem is different for different types of insomnia, or for different duration of symptoms.
- Fundamentally, insomnia symptoms from very different proposed underlying etiologies are very similar, and efficacy of treatments is measured with the same or highly similar endpoints measuring sleep latency and maintenance.
- Zolpidem acts on GABA receptors and regions of the CNS that are related to state of wakefulness, without any action known to be more specific to a specific etiology of insomnia.
- As noted in Section 3, Study LSH02 was a well-controlled trial of zolpidem immediate release in sleep laboratory ‘first night effect’ insomnia in patients 22- to 35 years old. The study examined doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 20 mg zolpidem, versus placebo, in 17 healthy males. Statistically significant reduction in sleep latency versus placebo was demonstrated for doses as low as 5 mg, with numerical superiority of the 2.5 mg dose. The findings from study LSH02 offer particularly compelling support for efficacy of the 5 mg dose in adult women because zolpidem exposure in adult men is *lower* than in adult women. Similarly, study 4054 in the Ambien CR development program showed efficacy for sleep latency in adult men and women from a controlled release formulation of zolpidem that in the first 30 minutes was similar to a 5 mg immediate-release dose. Study LSH08 showed efficacy of 7.5 mg zolpidem in adult men and women, providing additional evidence that doses lower than the currently recommended 10 mg dose are reasonable to recommend.

The sponsor additionally argued in a communication to DNP on August 22, 2012 that the lower doses for Ambien and Ambien CR recommended by DNP have not been shown to be effective, citing two studies that they assert were negative for the 5 mg dose, Study LSH08 and study LSH10. Study LSH08<sup>24</sup> (noted above for showing efficacy of the 7.5 mg dose), examined 5 mg Ambien, but did not show statistical significance for efficacy for that dose. DNP notes, however, that the 5 mg dose (N = 52) had only half the sample size of the 7.5 (N = 102) and 10 mg

<sup>23</sup> per International Classification of Sleep Disorders Manual classification

<sup>24</sup> Roth T et al (1995) *Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo*. Sleep 18:246-251

doses (N = 104), such that the sponsor's claim that 10 mg was effective while 5 mg was ineffective is biased by other experimental factors. Furthermore, the 5 mg dose enrolled only 16 women versus 36 men, such that no sound conclusions can be drawn about the efficacy of the 5 mg dose in women.

The sponsor states that study LSH10 'did not generally indicate effectiveness of the 5 mg dose'. The study enrolled 114 adult patients with chronic insomnia (71 females and 43 males, between 26 and 29 patients at each dose). DNP notes, however, that the p-value for the 1<sup>st</sup> night for the 5 mg Ambien dose appears to be 0.024,<sup>25</sup> and the effect size, 24 minutes improvement, was larger than the effect size for the 20 mg Ambien dose (22 minutes). Furthermore, the effect size for the 5 mg dose at day 7, 19 minutes, was very close to the effect size for the 20 mg dose, 21 minutes, and the lack of statistical significance for the 5 mg dose seems largely due to small sample size and larger baseline variability in latency to persistent sleep in the 5 mg arm versus the other arms. On night 7, the p-value for the 5 mg dose appears to have been 0.1, which may be the basis for the sponsor's assertion that study did not generally indicate effectiveness. While perhaps the study would not have been considered robust enough to be one of the required two pivotal studies generally required to support approval, DNP finds the evidence supportive of the 5 mg initial dose recommendation in adults.

The Division also finds pharmacokinetic evidence to provide compelling support for recommending the 6.25 mg dose of Ambien CR in adult women. The median zolpidem blood level associated with efficacy for sleep maintenance at 6 hours after dosing of the 12.5 mg dose in adult men was 44 ng/mL, and for women the median blood level after dosing the 6.25 mg dose is the same or higher, 47 ng/mL. The zolpidem level in women is also significantly higher than the level shown to be effective in elderly adults, about 29 ng/mL (from Sanofi response of September 26, 2011). There is no reason to believe that zolpidem levels in adult women that are as high, or higher than levels shown to be effective in adult men and in elderly men and women would not also be effective. Also, the 6.25 mg Ambien CR dose is reasonable to recommend for adult men, as, for example, 6-hour zolpidem levels in some men after the 6.25 mg dose are as high as 93 ng/mL (data from 28 October 2011 sponsor submission). More generally, across all time points and doses, adult women experienced a 2.6-fold higher exposure to zolpidem than adult men, indicating that the 6.25 mg dose is a well-supported dose. Finally, in study 4529 the change in PSG WASO for nights 1 and 2 was 19 minutes for both men and women, suggesting that the lower exposure achieved in men (versus the exposure in women) after the 12.5 mg dose is sufficient for

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<sup>25</sup> In the study LSH10 study report dated August 23, 1990, page 16, the table does have an asterisk indicating statistical significance for latency to persistent sleep for the 20 mg arm, but not for the 10 or 5 mg arm. In contrast, in the communication of August 8, 2012 from Sanofi to DNP, Ambien IR Attachment 2, LSH10 study results, the table indicates that the p-value for the 5 mg dose was 0.024, and for the 10 mg dose <0.001. DNP does not believe, however, that resolution of this apparent discrepancy is necessary to conclude that there is sufficient efficacy data to support the lower doses recommended for Ambien and Ambien CR.

efficacy for sleep maintenance, and that similar levels that occur after the 6.25 mg dose in women would likewise be effective for sleep maintenance.

## **6. Discussion and Recommendations**

As described in Section 3, driving impairment from zolpidem in a substantial minority of patients, mainly women, is likely to be as severe, or more severe, than that produced by alcohol at the legal limit of 'drunk driving'. This level of risk in patients that drive appears clearly to be unacceptable in the context of benefit from Ambien and Ambien CR. Revising currently recommended dosing, instructions for use, and warnings appears necessary to achieve an acceptable risk/benefit profile.

The Division proposed to the sponsor revised labeling that included both new safety warnings and a lower recommended dose in adult women, from 10 mg (Ambien) and 12.5 mg (Ambien CR) to 5 mg and 6.25 mg, respectively. The revised labeling also proposed expanding the recommended dose range for adult men, to include both the high and low doses above. For Ambien CR, morning blood levels in some patients are strikingly high, at or above the average C<sub>max</sub> of the drug. Even if the dose was reduced by half in all patients, about 5% would have morning zolpidem levels  $\geq 50$  ng/mL. Therefore, the Division concluded that labeling of Ambien CR should specifically discourage use in patients driving or engaging activities requiring full alertness the next morning.

## **Appendix**

### ***Epidemiological studies and risk of traffic accidents with sedative-hypnotic use***

Barbone F, McMahon AD, Davey PG et al. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998;352(9137):1331-1336.

Gibson JE, Rubbard RB, Smith CFP, Tata LJ, Britton JR, Forgarty AW. Use of self controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiology* 2009;169:761-768.

Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Morland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med* 2008;9(8):818-822.

Hooper TI, DeBakey SF, Pearse L, Pratt S, Hoffman KJ. The use of electronic pharmacy data to investigate prescribed medications and fatal motor vehicle crashes in a military population, 2002-2006. *Accid Anal Prev* 2010;42(1):261-268.

Orriols L, Philip P, Moore N et al. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. *Clin Pharmacol Ther* 2011;89(4):595-601.

Smink BE, Egberts AC, Lusthof KJ, Uges DR, de Gier JJ. The relationship between benzodiazepine use and traffic accidents: A systematic literature review. *CNS Drugs* 2010;24(8):639-653.

Neutel CI. Risk of traffic accident injury after a prescription for a benzodiazepine. *Ann Epidemiol* 1995;5(3):239-244.

Ravera S, van RN, de Gier JJ, de Jong-van den Berg LT. Road traffic accidents and psychotropic medication use in the Netherlands: A case-control study. *Br J Clin Pharmacol* 2011;72(3):505-13.

Yang YH, Lai JN, Lee CH, Wang JD, Chen PC. Increased risk of hospitalization related to motor vehicle accidents among people taking zolpidem: a case-crossover study. *J Epidemiol* 2011;21(1):37-43.

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/s/  
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RONALD H FARKAS  
01/06/2013

## **Clinical Review: Dosing for Zolpidem Products**

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<b>NDA:</b>	<b>19908, Ambien 21774, Ambien CR 21997, Edluar 22196, Zolpimist</b>
<b>Reviewer:</b>	<b>Ronald Farkas, MD, PhD Clinical Team Leader, Division of Neurology Products DNP/OND/CDER</b>

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### **1. Introduction**

The Division of Neurology Products (DNP) recently approved Intermezzo (NDA 22328), a sublingual formulation of zolpidem indicated when a middle-of-the-night (MOTN) awakening is accompanied by difficulty falling back asleep. DNP concluded that the recommended dose should be lower for women (1.75 mg) than for men (3.5 mg), because women clear zolpidem at a lower rate than men. This dosing was designed to minimize next-day psychomotor impairment, particularly next-day impairment of driving, while preserving efficacy for MOTN insomnia.

This review examines if dosing for the following zolpidem products approved for bedtime use appropriately minimizes next-day psychomotor impairment in women and men in the context of maintaining efficacy for insomnia characterized by difficulty initiating sleep:

- Ambien [immediate release (IR)] (5 and 10 mg tablets, NDA 19908), generic Ambien, and the following bioequivalent products
  - Edluar (sublingual tablet, 5 and 10 mg, NDA 21997)
  - Zolpimist (oral spray, 5 and 10 mg, NDA 22196)
- Ambien CR [controlled release] (6.25 and 12.5 mg tablets, NDA 21774), and generic Ambien CR.

An information request was sent to the sponsors of the above products on August 8, 2011 noting DNP concern that morning drug levels of hypnotic medications may remain high enough in some individuals or identifiable patient subgroups to impair driving to a degree that presents an unacceptable risk both to individuals and the public. DNP requested that the sponsors assess what is currently known about the pharmacokinetic and pharmacodynamic properties of their products, including differences that might arise due to demographic factors such as gender, age, ethnicity, etc. FDA also requested submission of pharmacokinetic datasets. These datasets, and additional datasets from generic

drug applications for zolpidem products, were used in the analyses described in this review.

## 2. Next-Day Psychomotor Impairment from Zolpidem

Next-day psychomotor impairment is of particular concern for insomnia drugs because a large percentage of patients drive the morning after dosing, and thus would potentially place both themselves and the community at risk if the chance of a motor vehicle accident (MVA) was increased by residual zolpidem levels. Both 'on-the-road' driving studies and laboratory-based psychomotor testing are used to assess if particular levels of drug cause impairment that plausibly would increase the risk of an MVA. Epidemiological studies measure risk of actual MVA in patients taking zolpidem, but are not informative about possible correlation between drug levels and risk, and are susceptible to confounding by factors other than use of the drug. The two types of evidence considered together, however, strengthen the connection between impaired performance from zolpidem and MVA risk.

### *Driving studies*

Data from an on-the-road driving study conducted in support of the Intermezzo NDA suggest that zolpidem blood levels above  $\approx 50$  ng/ml the morning after use may cause clinically important impairment of driving ability. The study was conducted by Dr. Vermeeren and associates at Maastricht University, with the primary endpoint based on 'on road' measurement of 'standard deviation of lateral position' (SDLP) during a 1 hour drive on the public highway. SDLP measures how well a subject is able to maintain the vehicle in a steady position relative to the left boundary of the driving lane. Since baseline SDLP differs for different individuals, drug effect is evaluated through change in an individual's SDLP after drug. A 'symmetry analysis' was used for the primary outcome, in which the proportion of subjects whose SDLP worsened was compared to the proportion of subjects whose SDLP improved to that same degree. If the proportion with impairment was greater than the proportion that improved, impairment would be suggested. The primary threshold change in SDLP chosen was 2.5 cm because, while this amount of change does not necessarily separate impaired from unimpaired drivers, it is the average impairment that has been reported in SDLP for drivers with a blood concentration of ethanol of 0.05%, a level that is the legal limit for driving in many countries (the legal limit is 0.08% in the United States). In addition, because the 2.5 cm change is not a 'bright line' of impairment, a range of thresholds between 1.75 cm and 6.5 cm were also examined.

For Intermezzo, analysis of SDLP by the symmetry analysis showed a statistically significant effect at 3 hours after the 3.5 mg dose, in a study with half men and half women. At the 2.5 cm threshold, roughly 25% of the patients experienced impairment (10 were 'impaired', 29 'unchanged', and 1 'improved'; see Appendix). On the premise that, in general, impairment increases with

increasing zolpidem blood levels, it thus seemed reasonable to conclude that roughly the highest 25<sup>th</sup> percentile of zolpidem blood levels would, experimental noise and other sources of variability aside, correlate with SDLP impairment. In women, who represent most of those with high zolpidem levels, the upper quartile blood level 3 hours after the 3.5 mg dose (in a separate PK studies) was roughly 45 ng/ml.

Results at 4 hours seemed to confirm the findings at 3 hours. While the symmetry analysis was not statistically significant at 4 hours, roughly 10% of subjects were nominally impaired (5 'impaired', 34 'neutral', 1 'improved'). At 4 hours, the upper 10<sup>th</sup> percentile of zolpidem blood levels in women was roughly 45 ng/ml (in a separate PK study), similar to the estimate for the impairing level at 3 hours. At larger SDLP thresholds of about 4- to 4.25 cm that correspond roughly to impairment from alcohol at the 0.08% legal limit for driving in the United States, results at 3 hours after Intermezzo suggested that about 10- to 15% of subjects were impaired. This would correspond to a zolpidem level of about 55 ng/ml. At 4 hours post-dosing, there was essentially no evidence of impairment at this SDLP level (1 'impaired' 39 'neutral', 0 'improved'). This is consistent with data from PK studies that zolpidem blood levels are usually below 55 ng/ml 4 hours after dosing, even in women.

Published studies using similar on-the-road driving tests generally support the above conclusions. Leufkens et al<sup>1</sup> found that about 5- to 6 hours after a MOTN dose of 10 mg zolpidem driving performance was 'moderately impaired', and Verster et al<sup>2</sup> found statistically significant impaired driving ability 4 hours after MOTN dosing of 10 mg zolpidem. While PK was not measured in these studies, *average* zolpidem level was likely about 25 ng/ml, with the positive findings for impairment likely generated by patients with above average (potentially far above average) zolpidem blood levels.

#### *Pharmacokinetic/pharmacodynamic studies*

In the drug development program for Ambien CR, a 10-way crossover PK/PD study was conducted with 8 doses/combinations of immediate-release and delayed-release zolpidem (study 4054). Patients (N=36) were given test drug before bed, and tested after awakening in the morning, at both 8 and 9 hours post-dose. Blood samples were collected at 8.5 hours post-dose. One PD endpoint was the Digit Symbol Substitution Test (DSST), a test of psychomotor performance that requires subjects to match symbols with corresponding digits. Performance on the test is affected by attention, perceptual speed, motor speed, visual scanning, and memory. Unlike the driving study described above that was conducted over a 1-hour test-period, the DSST is administered over a short period of time, 90 seconds. The test is therefore not designed to detect deficits in

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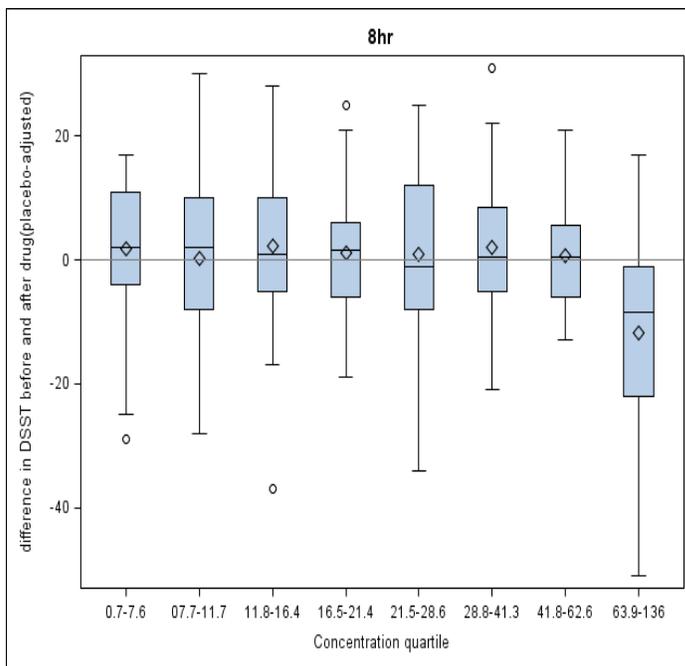
<sup>1</sup> Leufkens TR et al (2009) Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxodol, zopiclone and zolpidem. *J Sleep Res* 18:387-96.

<sup>2</sup> Verster JC et al (2002) Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *J Clin Psychopharm* 22:576-83.

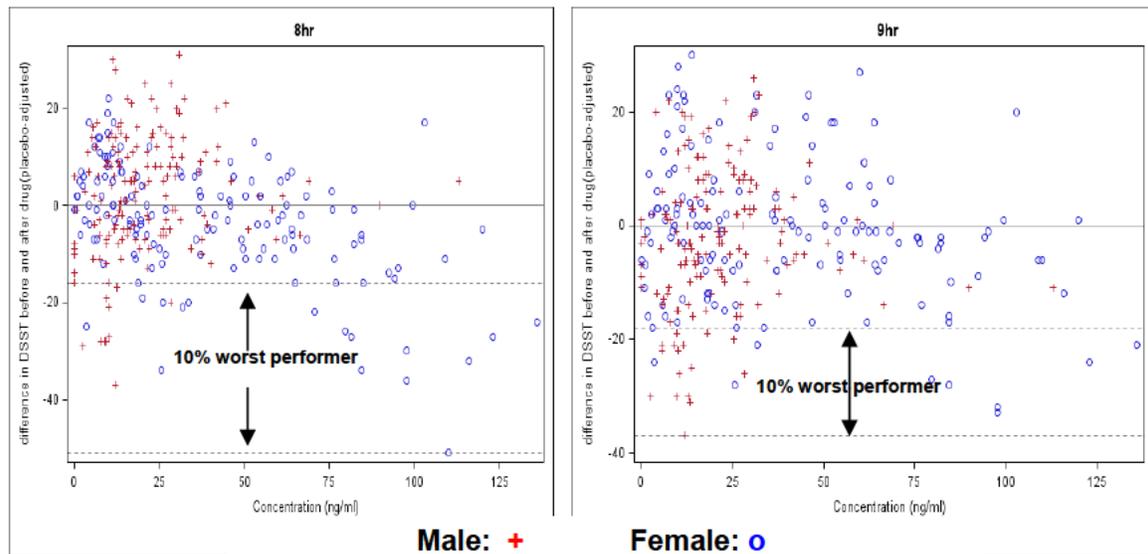
sustained attention, an important function for driving safety. The relationship between DSST and driving impairment is not well established, but in comparison, a blood alcohol concentration near the legal limit may correspond to impaired performance on the DSST of roughly 5- to 15%.

The DSST data was analyzed by Dr. Joo-Yeon Lee and Dr. Yaning Wang in the Division of Pharmacometrics (CDER/OTS/OCP). When  $\Delta\Delta$ DSST vs. concentration percentile was examined in 8 bins, a decrease in DSST of roughly 10 points (about 13% decline from average baseline), was present in the highest percentile bin, containing blood levels from about 65- to 135 ng/ml (Figure 1). A scatterplot of  $\Delta\Delta$ DSST vs. concentration by gender shows higher exposure in women (tests taken at both 8 and 9 hours after dosing shown), along with corresponding 'worse performance' mostly in women (Figure 2). Worsened performance on the DSST becomes apparent at roughly the lower end of the 65- to 135 ng/ml bin. Most of the subjects with high blood levels were women.

**Figure 1:  $\Delta\Delta$ DSST vs. concentration (8 hrs post-dose)**



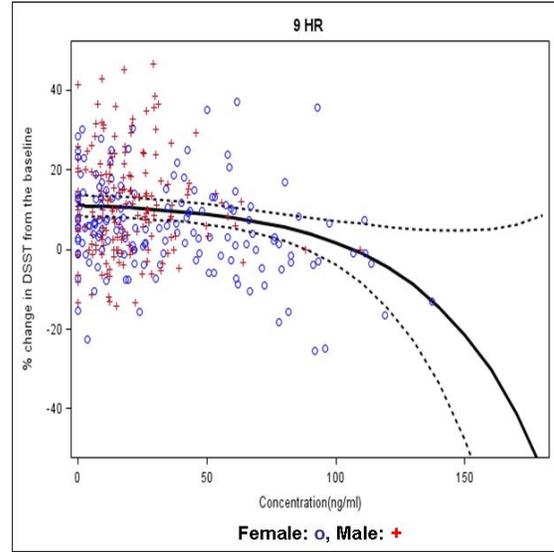
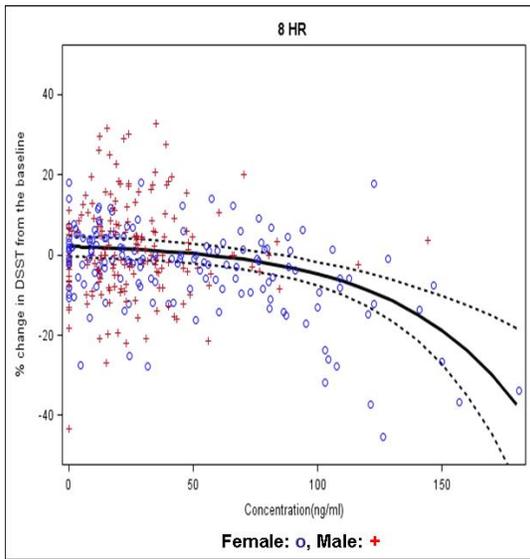
**Figure 2  $\Delta\Delta$ DSST vs. concentration by gender**



A 5% decrease in DSST occurs at roughly 75 ng/ml (a learning effect commonly occurs with serial testing of DDST, and may account for the percent change at the 9 hour test being greater than zero at low zolpidem concentration).

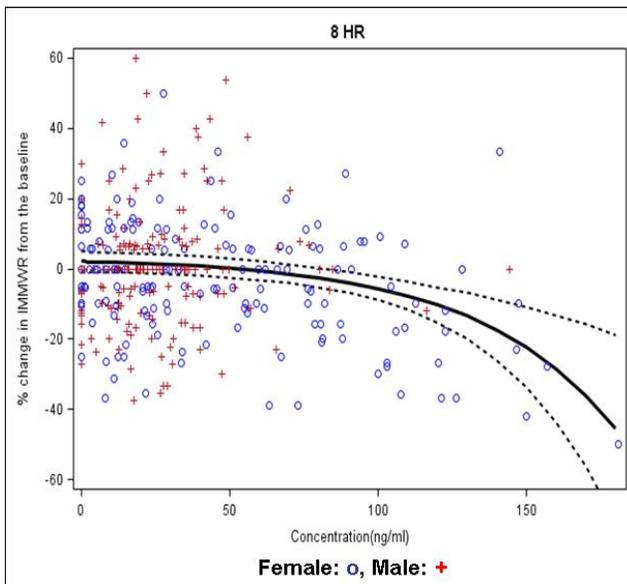
Figure 3 shows the same DSST data, analyzed by percent change, fit to a model assuming exponential increase of impairment with drug concentration. A 5% decrease in DSST occurs at roughly 75 ng/ml (a learning effect commonly occurs with serial testing of DDST, and may account for the percent change at the 9 hour test being greater than zero at low zolpidem concentration).

**Figure 3: Exponential Fit, % Change in DSST**



A similar degree of impairment of immediate word recall became apparent at about the same zolpidem blood level (Figure 4).

**Figure 4: Immediate Word Recall**



### Epidemiological Studies

A number of epidemiological studies suggest that insomnia medications increase the risk of next-day traffic accidents, as much as 4-fold after long-term use, and even more in the first few weeks of therapy. Dr. Simone Pinheiro (OSE/DEPI) conducted a high-level review of these studies, finding that most suggested an increase in motor vehicle accident risk with zolpidem, and that all reviewed studies suggested an association between benzodiazepine use (both anxiolytic and hypnotic use) and MVA risk. Dr. Pinheiro cautioned, however, that limitations of the studies, including potential confounding by indication, could not be excluded.

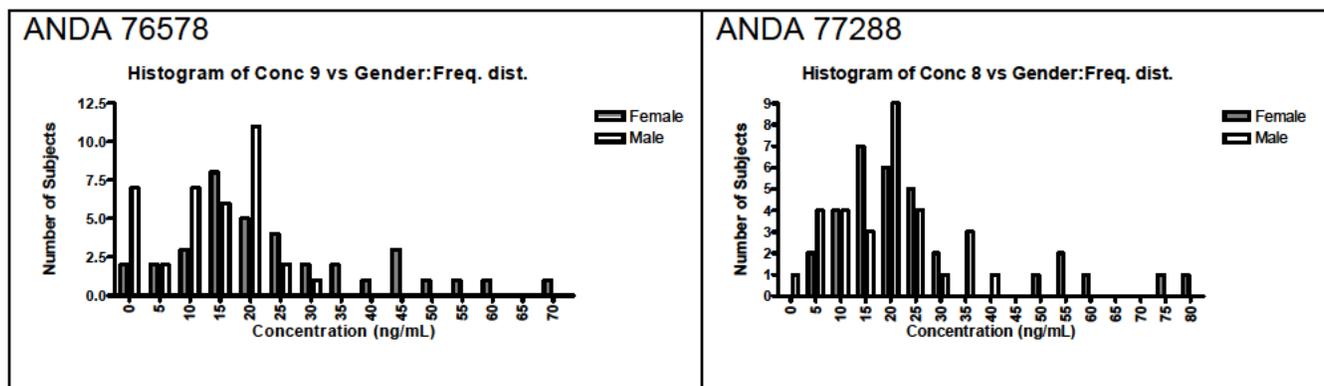
## 3. Occurrence of High Zolpidem Blood Levels During the Day

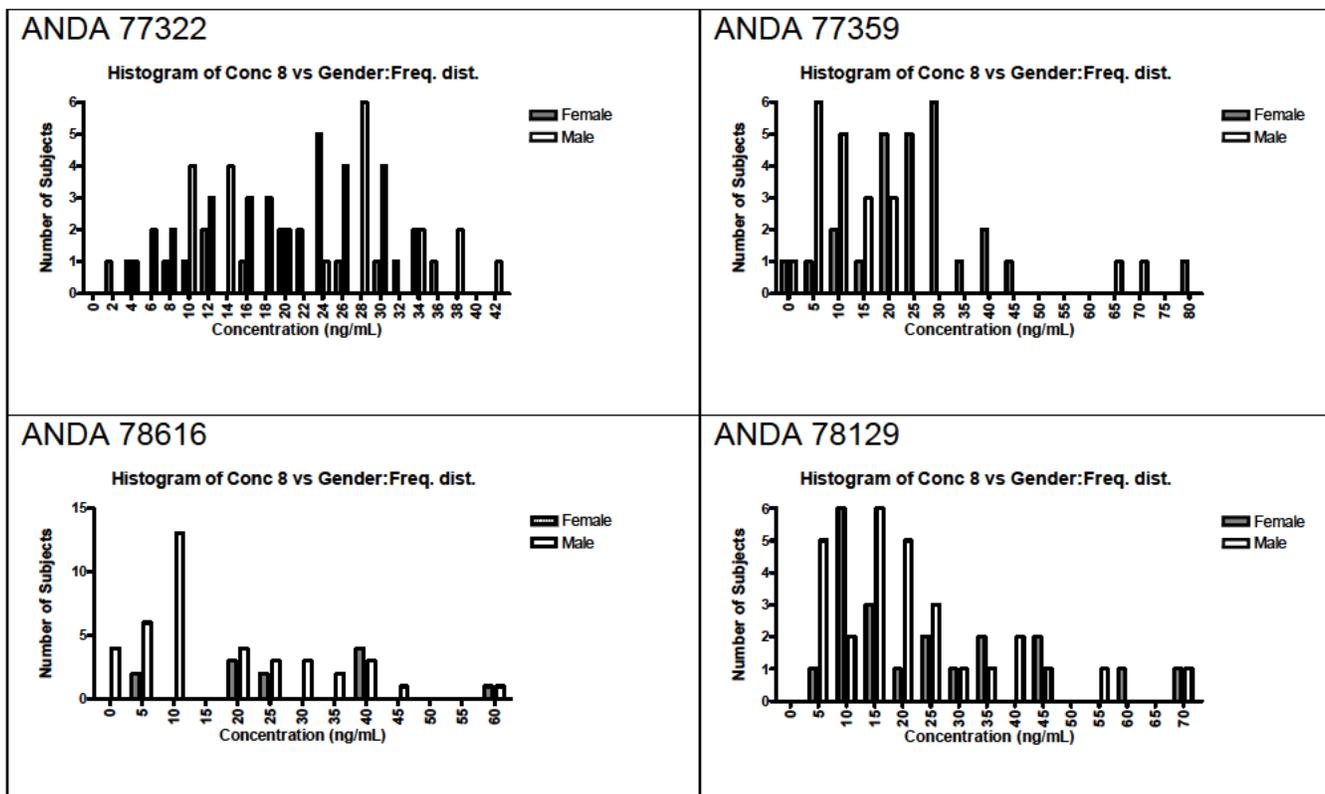
### *Ambien (immediate release), Morning blood levels*

As noted in Section 2, morning zolpidem levels beginning at roughly 50 ng/ml appear capable of impairing driving to a degree that increases the risk of MVA.

Figure 5 shows histograms of zolpidem concentration 8 or 9 hours (indicated in figure) after 10 mg Ambien or generic test drug, in a subset of ANDA studies. Findings were similar for Edluar and Zolpimist (not shown). There is wide inter-study variation, but generally a strong rightward skew towards high blood levels, in both men and women. However, a majority of subjects with zolpidem levels  $\geq 50$  ng/ml are women. In the total dataset of roughly 250 men and 250 women, with two PK measurements per patient (one for reference listed product and one for bioequivalent generic) about 15% of zolpidem measurements in women and 3% in men were  $\geq 50$  ng/ml at 8- to 9 hours post-dosing. This female/male ratio was similar at higher blood levels; for example 3 measurements in women and 1 in men were  $\geq 90$  ng/ml at this time point.

**Figure 5: Morning Zolpidem Levels, Ambien 10 mg**





*Ambien Cmax*

The incidence of many adverse effects of zolpidem increases sharply with dose over the relatively narrow range of doses studied (Table 1). While patients are generally in bed near zolpidem Cmax, this is not always the case, e.g. as many patients arise at night to urinate.

**Table 1**

INCIDENCE OF SELECTED ADVERSE EXPERIENCES BY DOSE IN SHORT TERM  
PLACEBO-CONTROLLED CLINICAL TRIALS  
(Percentage of Patients Reporting)

Adverse Experience	Placebo N=179	Ambien Dose				
		5.0 mg N=97	7.5 mg N=114	10 mg N=148	15 mg N=84	20 mg N=95
Dizziness	-	-	-	1	-	3
Drowsiness	-	1	-	2	5	7
Nausea	-	1	2	1	2	5
Vomiting	-	-	1	-	2	3
Amnesia	-	-	-	-	-	4

Table 1: from Original NDA Clinical Review, 1992, pg 37

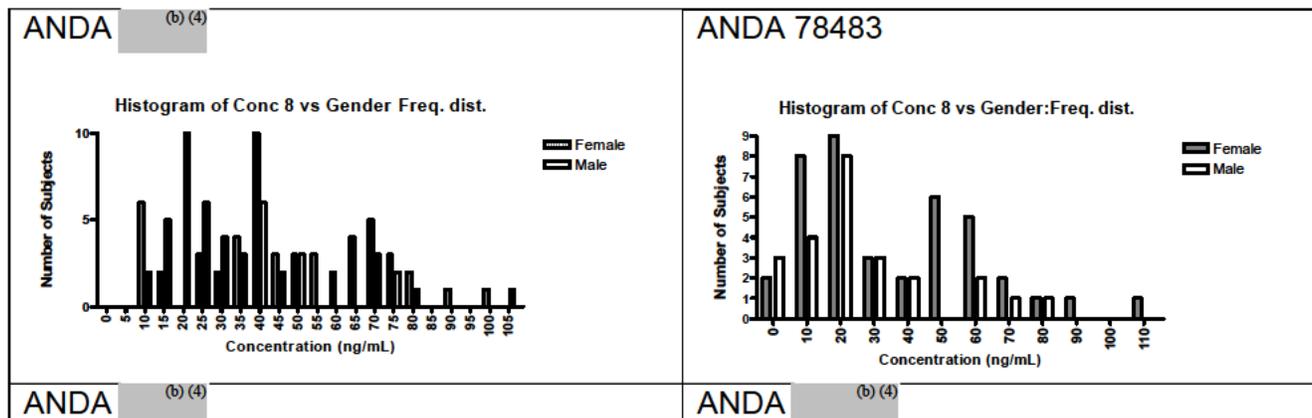
Objectively measured impairment of balance is positively correlated with zolpidem dose<sup>3</sup>. A positive association between zolpidem levels and more serious adverse events, like falls and hip fractures, is not well-established, but is plausible. Complex sleep-related behaviors associated with zolpidem such as sleep-driving also appear to be dose-related<sup>4</sup>. Adverse effects near Cmax for both Ambien IR and MR would likely be decreased by dosing recommendations that decreased exposures higher than necessary for efficacy.

*Ambien CR (controlled release), morning blood levels*

*12.5 mg dose*

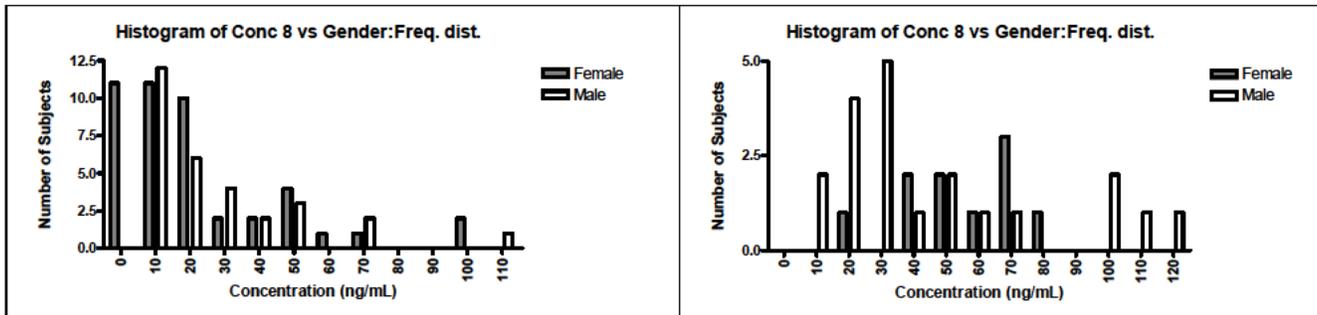
Figure 6 shows zolpidem levels 8 hours after dosing adults with Ambien CR 12.5 mg or generic equivalent. In about one third of measurements in women and about a quarter of measurements in men, zolpidem was  $\geq 50$  ng/ml. At higher levels there was no gender difference: about 5% of measurements were  $\geq 100$  ng/ml.

**Figure 6: Morning zolpidem levels, Ambien CR 12.5 mg**



<sup>3</sup> Rush CR and Griffiths RR. (1996) Zolpidem, triazolam, and temazepam: behavioral and subject-rated effects in normal volunteers. *J Clin Psychopharmacol* 16(2):146–57.

<sup>4</sup> Southworth et al (2006) Nonbenzodiazepine hypnotic use and cases of “sleep driving.” *Ann. Int. Med* 148(6):486-487.



In studies carried out by Sanofi to support the original approval of Ambien CR, the highest blood levels at 8 hours in a study including 93 women and 199 men was 187 ng/ml for women, and 117 ng/ml for men. Similarly, in another Sanofi study including 53 women and 34 men, the highest blood levels were 215 ng/ml and 165 ng/ml, respectively.

#### 6.25 mg dose

In a study of young subjects including 23 women and 47 men, the highest 8-hour zolpidem level after the 6.25 mg dose was about 95 ng/ml for both genders. In a study including 23 elderly women and 47 elderly men, the highest zolpidem levels were 76 ng/ml and 67 ng/ml, respectively.

## 4. Zolpidem Blood Levels and Efficacy

### *Ambien (immediate release)*

Zolpidem products are approved for sleep latency, an event that occurs temporally near and likely is largely driven by blood levels close to C<sub>max</sub>. The Ambien label notes that the average zolpidem C<sub>max</sub> is 121 ng/ml (in PK studies in men) after the 10 mg recommended adult dose. Figure 7 shows C<sub>max</sub> by gender for several ANDA PK studies for Ambien that enrolled both men and women. The studies generally show a higher C<sub>max</sub> than the study represented in the label, although data from ANDA 77359 is similar to the data represented in the Ambien label, suggesting that the 'lower than average' value was due to chance.

**Figure 7: C<sub>max</sub> by Gender, Ambien IR**

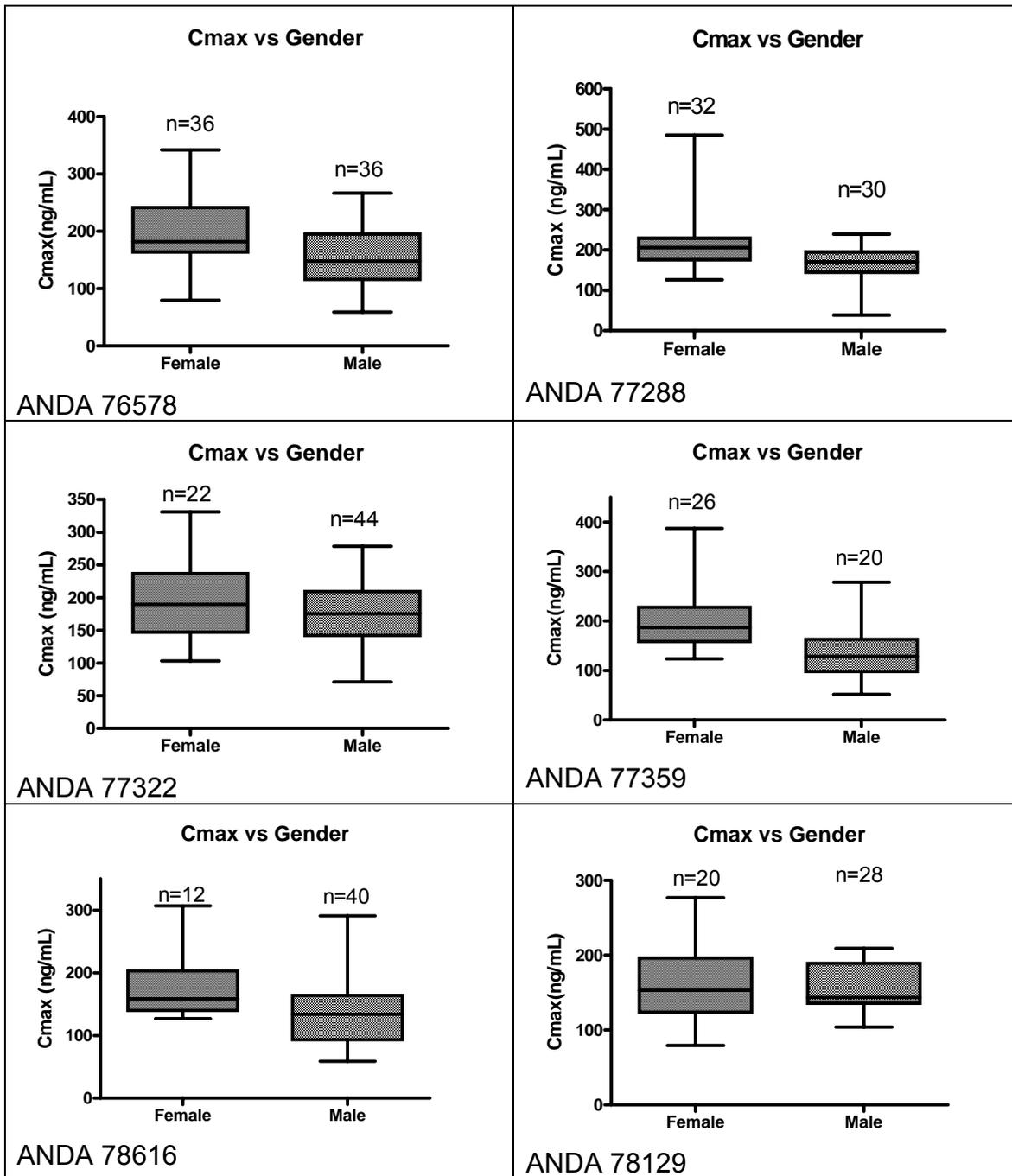


Figure 7 legend: median, quartiles, and highest/lowest values are shown.

No efficacy studies appear to exist of the 5 mg dose of zolpidem in adult chronic insomnia patients. In normal adult volunteers subjected to a model of acute insomnia in study 4054 (traffic noise + first night effect in a polysomnography laboratory), doses of zolpidem equivalent to 5 mg released in the first 30 minutes after dosing was statistically superior for sleep latency compared to placebo. In

elderly subjects (>70 years), C<sub>max</sub> is increased about 50%. Efficacy was demonstrated with the 5 mg recommended dose in elderly (>65 years), at a median C<sub>max</sub> of about 90 ng/ml. There is anecdotal evidence that elderly patients, at the same zolpidem exposure, exhibit greater pharmacodynamic sensitivity, but the magnitude (or even existence) of this effect is not well established. There is little evidence that men and women differ in pharmacodynamic sensitivity to otherwise equal exposures to zolpidem, but data addressing the issue is very limited.

Decreasing the recommended dose in women to 5 mg would produce a median C<sub>max</sub> about half as high as occurred in the studies shown in Figure 7, or roughly 80- to 90 ng/ml. If women with chronic insomnia respond similarly to the normal volunteers in the insomnia model mentioned above, the 5 mg dose would be effective in women. Similarly, if adult women with chronic insomnia responded similarly to patients >65 years old, the 5 mg dose would be effective in women. In particular, the 5 mg dose is likely to be effective in women somewhat younger than 65 years, since the 65-year cutoff does not represent a true cutoff point in drug level.

Concern might remain about efficacy from the 5 mg dose in women at the low end of the population exposure distribution. However, because of the compact shape of the low side of the exposure distribution, the lower 75<sup>th</sup> percentile exposure in women would actually be fairly close, within perhaps 10 ng/ml, of the median exposure in women, which is about 75 ng/ml. This suggests that efficacy would likely be preserved for most women taking the 5 mg dose.

In the development program for Intermezzo, a zolpidem drug approved for insomnia when a middle-of-the-night (MOTN) awakening is followed by difficulty returning to sleep, an average zolpidem C<sub>max</sub> of 37 ng/ml in women after a 1.75 mg zolpidem dose was found to be effective for shortening MOTN-sleep latency. While the relationship between zolpidem response for insomnia when first falling asleep versus response for MOTN insomnia is unknown, low blood levels of zolpidem clearly retain pharmacodynamic effect shortening sleep latency under generally similar conditions.

By design, efficacy studies for zolpidem (and most other drugs) can be positive even if patients at the low end of the population exposure curve obtain little or no benefit from the drug. At the 5 mg dose, the lowest zolpidem C<sub>max</sub> in the 148 female subjects in the studies in Figure 7 can be estimated to be about 35 ng/ml. This is about the same as the lowest C<sub>max</sub> in men after the 10 mg dose. Thus, to an approximation, the risk of poor efficacy due to low exposure for women taking the 5 mg dose would be similar, or only marginally higher, than the risk in men taking the 10 mg dose. As 10 mg has nevertheless been the recommended dose in men, the 5 mg dose (at least as an initial dose) appears similarly acceptable in women.

*Ambien CR (controlled release)*

The zolpidem blood level necessary during the middle part of the night to maintain sleep is not well defined. In addition, Ambien CR labeling conveys an apparent decrease of efficacy over the first weeks of treatment [emphasis added]:

'Ambien CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Ambien CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment.

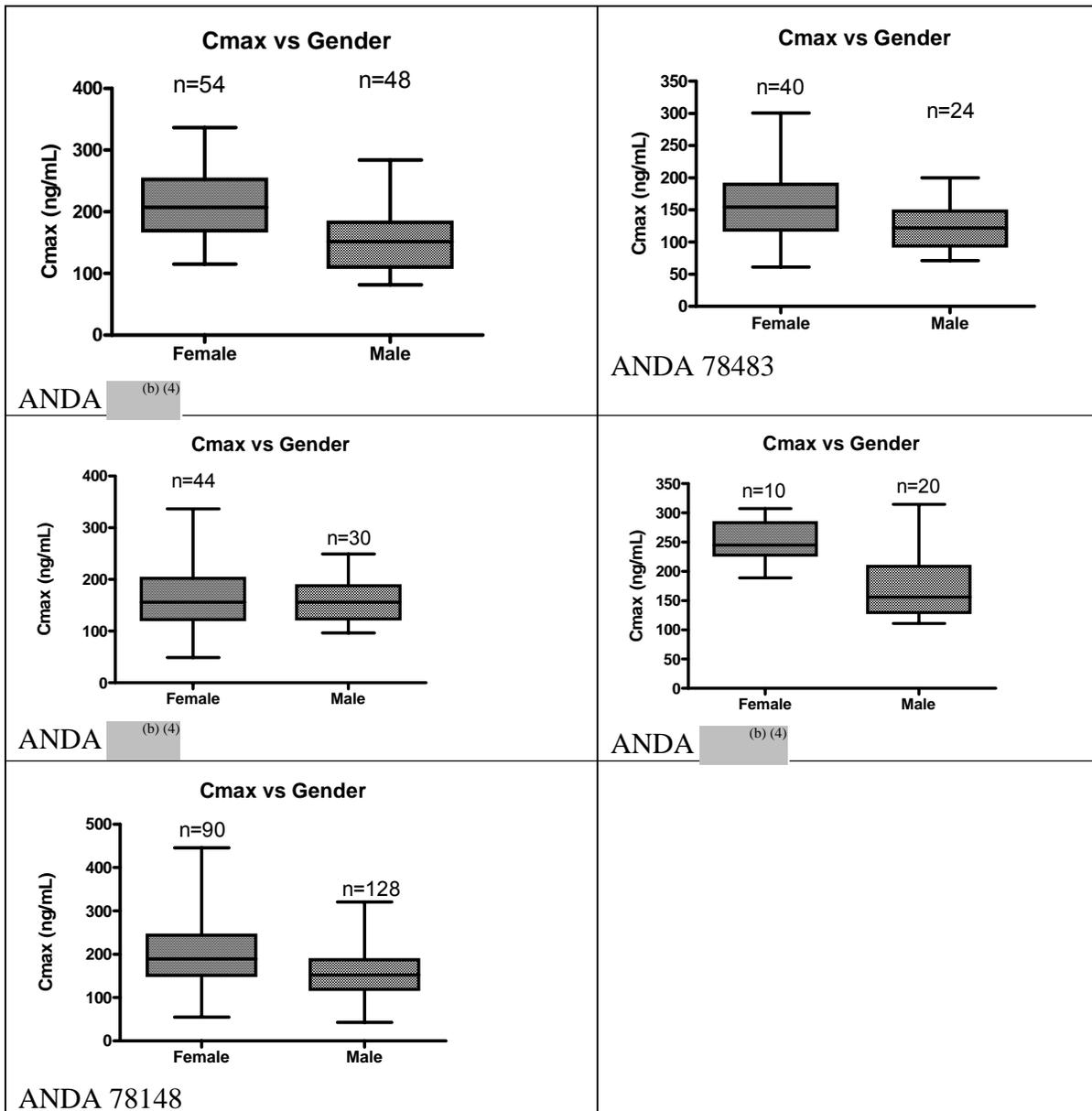
Elderly outpatients ( $\geq 65$  years) with primary insomnia (N=205) were evaluated in a double blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Ambien CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment.'

Further complicating the question of effective blood levels for sleep maintenance, Dr. Feeney noted in his clinical team leader review of the original Ambien CR NDA that *wake time* was greater for patients treated with Ambien CR than for placebo patients in hours 7 and 8 of nights 15 and 16, approaching an effect size equal to the benefit from Ambien CR seen during earlier hours of the night. This suggests that time from dosing and/or recent past blood levels (and perhaps other factors) affect efficacy for sleep maintenance.

Therefore, it does not seem possible to make any predictions about efficacy of Ambien CR if the current dosing recommendations are altered in an effort to avoid higher than desirable C<sub>max</sub> or morning zolpidem levels in patients at the high end of exposure.

Figure 8 shows zolpidem C<sub>max</sub> after dosing of ambien CR and bioequivalent generics at 12.5 mg. Zolpidem levels in patients at the high end of the distribution are  $> 400$  ng/ml, likely about 3-fold higher than necessary for efficacy for sleep initiation. Even though it isn't possible to conclude that the 6.25 mg dose would be effective for sleep maintenance in adults, dosing recommendations should still be designed to decrease the risk of adverse events in patients at the high end of the distribution of C<sub>max</sub>.

Figure 8: Zolpidem Cmax after Ambien CR 12.5 mg



## 5. Other Demographic Factors

DNP requested that the sponsors assess what is currently known about the pharmacokinetic and pharmacodynamic properties of their products, including differences that might arise due to demographic factors including age, weight, and ethnicity. Most subjects in PK studies were young adults, clustering around 20- to 30 years old, but with a significant minority between 40- and 60 years old. No relationship between blood level and age was evident in this range. Similarly, no relationship was discernable between body weight and blood level. There was adequate representation of African Americans in combined studies of zolpidem

products to conclude that zolpidem blood levels were not distinguishable from those in Caucasian's. The number of subjects from other ethnicities was too small to support any conclusions.

## 6. Discussion and Recommendations

### *Ambien and bioequivalent products*

The currently recommended 10 mg adult dose results in morning blood levels in roughly 15% of women and 3% of men that are likely to impair driving to a clinically meaningful degree. In a similar percentage of patients, C<sub>max</sub> may be high enough to increase the risk of potentially serious adverse events, including falls and complex sleep-related behaviors such as sleep-driving.

Patient's have poor insight into the level of their own impairment from psychoactive drugs, including zolpidem<sup>5,6</sup>. There is no evidence that safety concerns related to next-day residual drug levels are adequately addressed by instructing patients taking zolpidem to refrain from driving or other dangerous activities until they feel 'fully awake' or 'know how the drug affects them'. There might even be concern that such instructions promote *unsafe* drug use by conveying that driving is safe when drug levels are likely to be high so long as the patient 'feels fully awake.'

The correlation between tests of psychomotor function from zolpidem (including on-the-road driving tests) and actual MVA risk is not established. However, impairment from zolpidem at or above that produced by alcohol at the legal limit of 'drunk driving' on-face seemingly presents a clinically meaningful safety risk. Epidemiological studies additionally suggest association between zolpidem use and MVA risk.

Driving impairment has not been detected after careful testing of untreated insomnia patients, and treatment of insomniacs with hypnotics has not been found to improve driving performance<sup>7</sup>. While the therapeutic value of insomnia medications should still remain a consideration in evaluating the tolerability of risks from driving impairment from zolpidem, improved driving ability can *not* be considered a potential benefit of treatment.

### *Dosing Recommendations for Ambien and bioequivalent products*

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<sup>5</sup> Verster JC, Roth T (2011) Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. *Psychopharmacology (Berl)*

<sup>6</sup> Mallila MJ and Mattila-Evenden ME (1997) Effects of alcohol and hypnosedative drugs on digit-symbol substitution: comparison of two different computerized tests. *J. Psychopharmacology* 11:313-7.

<sup>7</sup> Leufkens T, Schumacher M, Bocca ML et al. (2011) Effects of medicinal drugs on actual and simulated driving. Driving under the influence of Drugs, Alcohol and Medicines Integrated Project. [http://www.druid-project.eu/cln\\_031/nn\\_107548/Druid/EN/deliverables-list/downloads/Deliverable\\_\\_1\\_\\_2\\_\\_2,templateId=raw.property=publicationFile.pdf/Deliverable\\_1\\_2\\_2.pdf](http://www.druid-project.eu/cln_031/nn_107548/Druid/EN/deliverables-list/downloads/Deliverable__1__2__2,templateId=raw.property=publicationFile.pdf/Deliverable_1_2_2.pdf)

It is generally true that the lowest effective dose of a drug for insomnia should be used, and that dosing should be individualized for the patient. However, effective individualized dosing of sleep drugs is difficult to achieve in the setting of current clinical practice. As noted above, subjective perception of impairment lacks the sensitivity expected of a clinically useful test. Importantly too, given the night-to-night variability in insomnia symptoms, and the amnestic and perception-altering effects of not only sleep drugs but sleep itself, the lowest effective dose similarly is difficult to establish.

Measuring zolpidem blood levels could seemingly provide useful information to guide dosing, particularly identifying patients with much higher than desirable exposure. However, additional data on usefulness and practicability would be needed before such an approach could be recommended. Instead, adjusting currently recommended dosing and instructions for use appears to achieve most safety and efficacy goals. This review recommends that the lowest effective dose of zolpidem be used, and that the 5 mg dose should not be exceeded in women unless clearly necessary for efficacy, and in the context of increased clinical monitoring. Initial dosing in men would be either 5 or 10 mg, depending on the clinical situation, with further dose adjustment as clinically indicated.

#### *Ambien CR and generic products*

A much higher percentage of both men and women, about 1 in 4 and 1 in 3, respectively, experience potentially impairing morning zolpidem levels after use of Ambien CR. Morning blood levels in some patients are strikingly high, at or above the average C<sub>max</sub> of the drug. It seems unlikely that any ordinary dosing instructions (i.e. short of measuring blood levels or residual psychomotor effects) could assure that most patients had exposures safe for next-day driving and other activities requiring full mental alertness. Therefore, labeling of Ambien CR should discourage use in patients engaging in such activities.

High C<sub>max</sub> and resultant increased risk of nighttime adverse events is still a concern for patients taking the 12.5 mg dose of Ambien CR, regardless of next-day activity. Initial dosing of 6.25 mg for both men and women may be warranted to address safety concerns, even at the cost of less than desired efficacy for sleep maintenance in a significant (but not well-defined, with available data) proportion of patients. As for Ambien, because of higher exposure in women compared to men, the dose of Ambien CR in women should not be increased unless clearly necessary for efficacy, and in the context of increased clinical monitoring.

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/s/  
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RONALD H FARKAS  
05/29/2012

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**019908Orig1s032s034**

**021774Orig1s013s015**

**OTHER REVIEW(S)**

## REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 19908/S-034, 21774/S-015  
Safety Labeling Change (SLC) Supplements

**Name of Drug:** Ambien (zolpidem tartrate) 5 mg and 10 mg Tablets  
Ambien CR (zolpidem tartrate) 6.25 mg and 12.5 mg Tablets

**Applicant:** Sanofi US, Bridgewater, NJ 08807

### Labeling Reviewed

**Submission Date:** April 4, 2013

**Receipt Date:** April 4, 2013

### Background and Summary Description

**Ambien (NDA 19908)** was approved on December 16, 1992.

Active Ingredient: Zolpidem Tartrate

- Indication of Use: Treatment of insomnia
- Route of Administration: Oral Tablet
- Dosage Form: Tablet
- Strength: 5 mg, 10 mg
- Dose and Frequency: taken nightly for short term insomnia characterized by difficulty with sleep (b) (4)

**Ambien CR (NDA 21774)** was approved on September 2, 2005.

Active Ingredient: Zolpidem Tartrate (extended release)

- Indication of Use: Treatment of insomnia characterized by difficulties with sleep onset and/or maintenance
- Route of Administration: Oral Tablet
- Dosage Form: Tablet
- Strength: 6.25 mg, 12.5 mg
- Dose and Frequency: taken nightly for insomnia characterized by difficulty with sleep onset and /or maintenance

The Division of Neurology Products (DNP) issued a Safety Labeling Change (SLC) request letter on January 9, 2013 for Ambien (zolpidem tartrate) 5 and 10 mg Tablets and Ambien CR

6.25 mg and 12.5 mg Tablets. This was part of a labeling change for all zolpidem tartrate products, except for Intermezzo (NDA 22328), where the changes have already been in place since Intermezzo approval.

There were other changes to the label based on the clinical review for Ambien 19908/S-034 and 21774/S-015. Please refer to those reviews for additional information (Dr. Ron Farkas review memos dated 9/4/12, 1/6/13, 2/22/13, and 3/15/13).

In response to the SLC request, Sanofi US submitted a rebuttal on February 7, 2013. DNP granted a labeling discussion extension on March 8, 2013.

The main reason for the SLC was that DNP had become aware of recent findings from studies conducted for driving simulation and functional impairment trials that included measurement of zolpidem blood levels after dosing. The findings were as follows:

1. Morning zolpidem blood levels after use of zolpidem 10 mg are high enough in some people, especially women, to impair driving.
2. Zolpidem blood levels in excess of 50 ng/mL impair driving ability; the degree of impairment is similar to that observed with ethanol blood levels that are illegal for driving, and widely recognized as having the potential for an increase in the risk of traffic accidents, traffic-related injuries, and deaths.
3. Publications describing driving simulation or psychomotor test studies support that the impairment in driving ability is often not recognizable to the affected individual.

DNP considered the above information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA, thus the SCL was requested. After the sponsor submitted a rebuttal argument on February 7, 2013, a series of informal telecons were held. Labeling agreements were reached for both products.

The new agreed-upon text for the Dosage and Administration section is:

**Ambien (zolpidem tartrate tablets)**

**2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien should be individualized~~

**2.1 Dosage in Adults**

~~The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Ambien dose should not exceed 10 mg per day. Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities~~

that require full alertness [see Warnings and Precautions (5.1)]. The total dose of Ambien should not exceed 10 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

## **Ambien CR (zolpidem tartrate extended-release tablets)**

### **2 DOSAGE AND ADMINISTRATION**

~~The dose of Ambien should be individualized~~

#### **2.1 Dosage in Adults**

~~The recommended dose of Ambien CR for adults is 12.5 mg once daily immediately before bedtime. The total Ambien CR dose should not exceed 12.5 mg per day. Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [see Warnings and Precautions (5.1)]. The total dose of Ambien CR should not exceed 12.5 mg once daily immediately before bedtime.~~

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

There were additional changes suggested by the sponsor in their April 4, 2013 supplement. The changes are listed below and refer to both Ambien and Ambien CR (except where indicated):

### **HIGHLIGHTS (HL)**

1. RECENT MAJOR CHANGES:

Sponsor proposed deletion of “Use in Specific Populations including gender differences (8) and (8.6)” since sponsor believes this is in accordance with (201.57(a)(5) and (c)(1)(2)(3)(5)(6).

2. DOSAGE AND ADMINISTRATION

- Sponsor proposed to include “initial” and “with at least 7-8 hours remaining before the planned time of awakening” to be consistent with the language in 2.1
- Sponsor proposed repositioning “Geriatric patients and patients with hepatic impairment”

before “Lower doses of CNS” to be consistent with FPI.

- [REDACTED] (b) (4)

3. WARNINGS AND PRECAUTIONS

- Sponsor edited several cross-references.
- Sponsor proposed repositioning “Respiratory Depression” statement before “Withdrawal Effects” to be consistent with FPI.

4. DRUG INTERACTIONS

Sponsor proposed revising “effects” to read “effect” for consistency between Ambien and Ambien CR.

5. USE IN SPECIFIC POPULATIONS (Ambien CR only):

Pediatric Use: Sponsor revised 7.4% to 7% as stated in section 8.4

**The Team Leader agreed to the above changes in Highlights (HL), with the exception of some of the cross references in WARNINGS AND PRECAUTIONS, referring to a new subsection, the addition of which was subsequently rejected.**

**FULL PRESCRIBING INFORMATION CONTENTS**

Sponsor proposed adding a new subsection “5.2 [REDACTED] (b) (4) [REDACTED]”.

**The Team Leader rejected** this new section stating that dividing the section on daytime effects separates similar, and in some cases identical warnings.

**FULL PRESCRIBING INFORMATION (FPI)**

**2 DOSAGE AND ADMINISTRATION**

**2.2 Special Populations**

Sponsor proposed revising “normal” to read “normal subjects” for consistency between Ambien and Ambien CR.

**Team Leader agreed.**

**2.3 Use with CNS Depressants**

Sponsor proposed revising “adjustments” to read “adjustment” for consistency between Ambien and Ambien CR.

**Team Leader agreed.**

## **5 WARNINGS AND PRECAUTIONS**

Sponsor proposed to include subheading 5.2 to enhance clarity.

**Team Leader rejected** (see reason given above under FULL PRESCRIBING INFORMATION CONTENTS).

### **5.4 Abnormal Thinking and Behavioral Changes**

Sponsor proposed revising “symptoms also occur” to read “symptoms may also occur” for consistency between Ambien and Ambien CR.

**Team Leader agreed.**

### **5.6 Respiratory Depression**

Sponsor proposes to revise “risks” to read “risk” for consistency between Ambien and Ambien CR

**Team Leader agreed.**

## **6 ADVERSE REACTIONS**

Sponsor proposed changes to cross referencing to include new subsection in Warnings and Precautions 5.2.

**Team Leader rejected** (see reasons noted above under FULL PRESCRIBING INFORMATION CONTENTS).

## **7 DRUG INTERACTIONS**

### **7.2 Drugs that Affect Drug Metabolism via Cytochrome P450**

Sponsor proposed adding “drugs on” for consistency between Ambien and Ambien CR.

**Team Leader agreed.**

## **8 USE IN SPECIFIC POPULATIONS (AMBIEN CR ONLY)**

### **8.4 Pediatric Use**

Sponsor proposed adding “CR” and retaining “of zolpidem” for consistency between Ambien and Ambien CR.

**Team Leader agreed.**

## **12 CLINICAL PHARMACOLOGY**

- Sponsor proposes to retain the subsection (b) (4) since this is useful information for the physician.

**Team Leader rejected.** Under new PLR guidance, we do not support negative (b) (4) statements in Section 12. Only when positive interactions are reported are we able to include information and it would be under the Warnings and Precautions section, not Section 12.

- Sponsor proposed leaving certain high-lighted text in the (b) (4) section:

**Team Leader rejected**, stating the information is redundant.

In addition, for Section 7.1 there was one change the Review team suggested adding after reviewing changes submitted from another zolpidem NDA. The change is to add:

“Chlorpromazine” in header for second paragraph and cross references to Clinical Pharmacology 12.3 to second, third and fifth paragraphs.

**The sponsor agreed to this change.**

## **MEDICATION GUIDE - Ambien IR**

1. **What is the most important information I should know about AMBIEN?**  
Sponsor proposed adding “Take AMBIEN right before you get in bed, not sooner.”

**The Team Leader agreed.**

2. Sponsor edited “doctor” replacing it with “healthcare provider” in 2 sentences.

**The Team Leader agreed.**

## **MEDICATION GUIDE - Ambien CR**

1. **What is the most important information I should know about AMBIEN CR?**

For consistency with Ambien, the sponsor proposed adding:

- **Do not take more AMBIEN CR than prescribed.**
- **Do not take AMBIEN CR unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take AMBIEN CR right before you get in bed, not sooner.**

**The Team Leader agreed.**

2. **After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as...**

Sponsor proposed adding: “vomiting”.

**The Team Leader agreed.**

3. Sponsor edited “doctor” replacing it with “healthcare provider” in 1 sentence.

**The Team Leader agreed.**

There were also minor format changes to the package insert and Medication Guide.

### **Conclusions/Recommendations**

The changes to the package insert and medication guide have been reviewed and concurred to by Ron Farkas, MD, PhD, Team Leader (as noted throughout this review).

Cathleen Michaloski, BSN, MPH

4/17/13

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Sr. Regulatory Project Manager

Date

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/s/  
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CATHLEEN B MICHALOSKI  
04/18/2013

JACQUELINE H WARE  
04/18/2013