

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019908Orig1s025

Trade Name: AMBIEN

Generic or Proper Name: Zolpidem tartrate

Sponsor: Sanofi-Aventis

Approval Date: October 4, 2007

Indication: Ambien 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

019908Orig1s025

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019908Orig1s025

APPROVAL LETTER



NDA 19-908 S-020, S-024, S-025

Sanofi- Synthelabo Research
Attention: Daryl DeKarske, MPH
9 Great Valley Parkway
Malvern, PA 19355

Dear Mr. DeKarske:

Please refer to the supplemental new drug applications noted below submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ambien (zolpidem tartrate) Tablets.

Application	Submitted on:	Received on:	Provides for:
S-024	March 27, 2007	March 28, 2007	“Changes Being Effected” Supplement; revisions to Overdose section.
S-025	August 14, 2007	August 15, 2007	“Prior Approval” Supplement: Medication Guide.

We note that Supplemental Application **S-025** was submitted in response to an Agency request included in a December 4, 2006 letter.

We have completed our review of supplemental application (**S-025**) and it is approved, effective on the date of this letter.

Additionally, we have completed our review of Supplemental Application (**S-024**) and have determined that it is approvable. However, after review of your proposed Package Insert included with this supplement, we have determined that additional modifications are needed. Before supplement **S-024** may be approved, you must address the deficiencies described below.

Additional Labeling Changes

- In section 4.1, (b) (4) section 5.2 Severe anaphylactic and anaphylactoid reactions).
- Your proposal to add the following sentence, “Ambien should be used with caution in patients with sleep apnea syndrome and myasthenia gravis” is acceptable.
- In section 5.3, please remove the brackets around the last two sentences in the first paragraph, i.e. the sentences describing the incidence of hallucinations seen in the clinical trials. Additionally there should be a cross reference to section 8.4 where the pediatric trial is described in detail. In the second paragraph of this section, the first sentence should read as follows:

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 with

(b) (4)

The last sentence of this paragraph should be made a stand alone paragraph and should be altered to read as follows:

Worsening of depression, including suicidal thoughts and actions (including completed suicides) has been reported in association with the use of sedative hypnotics.

- In section 6.1, we note that you have deleted the heading “Incidence in controlled clinical trials”. We ask that you reinstate this heading for 6.1.
- Final paragraph of section 7.1 CNS-active drug should become the initial paragraph in this section.
- The two paragraphs in section 7.2 should be reversed.
- The sentence “Ambien should not be administered with or immediately after a meal” should be included in the DOSAGE AND ADMINISTRATION section of the PI and in the SAFE USE OF SLEEPING MEDICINES section of the information for patients section.
- The subheading “non-teratogenic effects” in section 8.1 Pregnancy should be bolded.
- The pediatric use section of the label (section 8.4) should read as follows:

(b) (4): Safety and effectiveness (b) (4) have not been established. In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder were treated with an oral solution of zolpidem. Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%). Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

- The addition of the following sentences to the overdose section (section 10.1) is acceptable:
 - 1) In post marketing experience of overdose with zolpidem 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, 2) however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).
- In section 10.2, the subheading “poison control center” should be deleted.

- In section 12.3, the entire paragraph entitled “Postulated relationship between elimination rate of hypnotics and their profile of common untoward effects” should be deleted.
- In section 14.2, the references to the doses studied should be removed. While the section may continue to make reference to the findings with the 10 mg dose, all references to the 15 mg dose should be removed. The following sentence should be added to the end of this section:

Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with (b) (4) (b) (4) (b) (4) Ambien.

- The heading for section 17.1 should be changed to read: (b) (4). The first sentence in this section, “Patient information is printed at the end of this insert” is to be deleted.
- In the subsection of section 6 entitled “Adverse events observed at an incidence of $\geq 1\%$ in controlled trials,” the first sentence should read: The following tables enumerate treatment-emergent adverse event 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.
- The tables in the adverse event section should be modified to read as follows:

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
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

Please note that we have attached to this letter labeling that includes the approved Medication Guide (**S-025**) and all of the additional revisions to the package insert (in ~~strikeout~~/redline format) discussed above. We ask that you submit final printed labeling (FPL) that is identical to this labeling.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

With regard to Supplemental Application S-024:

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

With regard to “approved” Supplemental Application S-025:

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplemental application NDA 19-908 S-025.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit revised content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at the following website:

<http://www.fda.gov/oc/datacouncil/spl.html>

Supplemental Application S-020:

We note that you provided a complete response to our December 4, 2006 approvable letter to supplemental application **S-020** on March 7, 2007. However, we also note that all of the proposed changes included in that submission were approved in our action letter sent to NDA **19-908/S-022** on March 28, 2007. Therefore, we will not complete a review of this supplemental application and it will be retained in our files with no further action.

NDA 19-908 S-020, S-024, & S-025

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

If you have any questions, call Cathleen Michaloski, MPH, Regulatory Project Manager, at 301-796-1123.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD

Director

Division of Neurology Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosure: Package Insert including Medication Guide

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

/s/

Russell Katz

10/4/2007 04:40:30 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019908Orig1s025

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 for oral administration 
Initial US Approval: 1992

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

Indications and Usage (1) 03/2007
Warnings and Precautions (5) 03/2007

-----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. (1)

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

- Adult dose: 10 mg immediately before bedtime (2.1)
- Elderly/Debililitated patients/Hepatic Impairment: Initial dose of 5 mg (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants (2.3)
- Total daily dose should not exceed 10 mg (2.4)

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

5 mg and 10 mg tablets (3)

-----CONTRAINDICATIONS-----

Hypersensitivity to zolpidem tartrate or inactive ingredients (4.1)

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

- Reevaluate if insomnia persists after 7 to 10 days of use (5.1)
- Severe anaphylactic and anaphylactoid reactions have been reported (5.2)
- Abnormal thinking, behavior changes and complex behaviors such as sleep-driving have been reported (5.3)
- Pediatric patients with attention-deficit/hyperactivity disorder (ADHD): Hallucinations (7.4%) and other psychiatric and/or nervous system adverse events were observed frequently (5.6, 8.4)
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose (5.3, 5.6)

- Withdrawal symptoms may occur with rapid dose reduction or discontinuation (5.4)
- CNS depressant effects, additive effects with CNS depressants (2.3, 5.5)
- Potential impairment of activities requiring complete mental alertness such as operating machinery or driving a motor vehicle, after ingesting the drug and the following day (5.5)
- Additive effects with alcohol; should not be taken with alcohol (5.5)
- Elderly/debililitated patients: Impaired motor, cognitive performance after repeated exposure, increased sensitivity (2.2, 5.6)
- Caution advised in patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, mild to moderate sleep apnea (5.6)

-----ADVERSE REACTIONS-----

- Most commonly observed adverse events in studies with zolpidem (up to 10 mg) at statistically significant differences from placebo were:
Short-term (<10 nights): Drowsiness, dizziness, and diarrhea
Long-term (28 - 35 nights): Dizziness and drugged feelings (6.1)
- Dose relationship observed for adverse events especially CNS and GI events (6.1)
- Other adverse reactions, including serious adverse reactions, have been reported (6)

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>

-----DRUG INTERACTIONS-----

- Imipramine: decreased alertness (7.1)
- Chlorpromazine: impaired alertness and psychomotor performance (7.1)
- Alcohol causes additive psychomotor impairment (7.1)
- Rifampin (CYP450) decreases exposure to, and effects of zolpidem (7.2)
- Sedative/hypnotic effect reversed by flumazenil (7.3, 10.2)

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

- Labor and delivery: No established use (8.2)
- Nursing mothers: Not recommended (8.3)
- Pediatric use: Safety and effectiveness have not been established (8.4)
- Geriatric use: Reduced dose in elderly to decrease side effects (8.5)

See 17 for PATIENT COUNSELING INFORMATION. The Medication Guide is printed at the end of this document.

{October 2007}

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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

The dose of Ambien should be individualized.

The recommended dose for adults is 10 mg immediately before bedtime.

2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of Ambien (zolpidem tartrate). Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients [*see Warnings and Precautions (5)*].

2.3 Administration with CNS depressants:

Downward dosage adjustment may be necessary when Ambien is administered with agents having known CNS-depressant effects because of the potentially additive effects [*see Warnings and Precautions (5)*].

2.4 Maximum daily dose:

The total Ambien dose should not exceed 10 mg per day.

3 DOSAGE FORMS AND STRENGTHS

Ambien is available in 5 mg and 10 mg strength tablets for oral administration.

Ambien 5 mg tablets are capsule-shaped, pink, film coated, with, AMB 5 debossed on one side and 5401 on the other. The 10 mg tablets are capsule-shaped, white, film coated, with AMB 10 debossed on one side and 5421 on the other. Tablets are not scored.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Ambien is contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 General

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 Ambien. Because some of the important adverse effects of Ambien appear to be dose related [*see Dosage and Administration (2)*], it is important to use the smallest possible effective dose, especially in the elderly.

5.2 Severe anaphylactic and anaphylactoid reactions

Rare 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 Ambien. 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 Ambien should not be rechallenged with the drug.

5.3 Abnormal Thinking and Behavioral Changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation and depersonalization. [In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4 % of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations.]

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. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with Ambien alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien appears to increase 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 occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

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.

5.4 Withdrawal effects

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs [*see Drug Abuse and Dependence (9)*].

5.5 CNS depressant effects

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Ambien showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

5.6 Special Populations

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg in such patients [*see Dosage and Administration (2)*] to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien (zolpidem tartrate) in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of Ambien in normals 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 Ambien (10 mg) when compared to placebo. However, precautions should be observed if Ambien is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Ambien should be used with caution in patients with sleep apnea syndrome or myasthenia gravis. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with Ambien did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored [*see Pharmacokinetics (12.3)*]. A study in subjects with hepatic impairment did reveal prolonged elimination in this group;

therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in depression: As with other sedative/hypnotic drugs, Ambien should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional over-dosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Pediatric patients: Safety and effectiveness of zolpidem have not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [*see Use in Specific Populations: Pediatric Use (8.4)*].

5.7 Laboratory tests

Monitoring: There are no specific laboratory tests recommended to monitor zolpidem levels.

Interference with laboratory tests: Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

6 ADVERSE REACTIONS

Serious adverse reactions including severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavior, complex behaviors, withdrawal effects, amnesia, anxiety, other neuropsychiatric symptoms and CNS-depressant effects have been reported with zolpidem [*see Warnings and Precautions (5)*].

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 clinical event. Events 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 event. Events 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 events in controlled trials: During short-term treatment (up to 10 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events 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 events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Adverse events observed at an incidence of $\geq 1\%$ in controlled trials: The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien 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 a pool 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 Short-term
Placebo-Controlled Clinical Trials**
(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		
Nausea	2	3
Diarrhea	1	-
Musculoskeletal System		

Myalgia	1	2
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*Events reported by at least 1% of Ambien patients are included

The following table was derived from a pool 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 Long-term
Placebo-Controlled Clinical Trials**
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back Pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Fatigue	1	2
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	-
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1

*Events reported by at least 1% of patients treated with Ambien.

**Incidence of Treatment-Emergent Adverse Experiences in Long-term
Placebo-Controlled Clinical Trials (*continued*)**
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10mg) (N=152)	Placebo (N=161)
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory System		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary tract infection	2	2

*Events reported by at least 1% of patients treated with Ambien

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

Adverse event incidence across the entire preapproval database: Ambien (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: 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, 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, insomnia, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, 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: hiccup. Infrequent: 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: 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, hypercholesterolemia, 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: Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, 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: Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

6.2 Postmarketing Experience

In addition to adverse events reported in clinical trials, angioneurotic edema has been reported spontaneously in postmarketing experience.

7 DRUG INTERACTIONS

7.1 CNS-active drugs

Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. 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. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated [*see Warnings and Precautions: CNS depressant effects (5.5)*].

A single-dose interaction study with zolpidem 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 at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following five consecutive nightly doses of zolpidem 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.

Since the systematic evaluations of Ambien (zolpidem tartrate) in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

7.2 Drugs that affect drug metabolism via cytochrome P450

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last dose of rifampin 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.

7.3 Other drugs

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg base/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal and embryofetal toxicity was 4 mg base/kg/day (between 4 to 5 times the MRHD of Ambien on a mg/m^2 basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (over 35 times the MRHD of Ambien on a mg/m^2 basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternebrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was

below 1 mg base/kg/day (< 2-times the MRHD of Ambien on a mg/m² basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day (between 9 and 10 times the MRHD of Ambien on a mg/m² basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg and higher. Decreased maternal body weight gain as well as evidence on non-secreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg and higher and decreased pup survival at maternal doses of 100 mg base/kg. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg (between 4 to 5 times the MRHD of Ambien on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Ambien should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nonteratogenic effects. Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

8.2 Labor and delivery

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

8.3 Nursing mothers

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

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

The use of Ambien in nursing mothers is not recommended.

8.4 Pediatric use

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, 0.25 mg/kg/day, up to a maximum of 10 mg/day (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%),

headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) [see *Warnings and Precautions: Special Populations (5.6)*]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

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 events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (ie, they could be considered drug related).

Adverse Event	Zolpidem	Placebo
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 ≥ 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses > 10 mg.

The recommended dose of Ambien is 5 mg in elderly to decrease the possibility of side effects [see *Dosage and Administration (2) and Warnings and Precautions (5)*].

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. 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. 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 Ambien (zolpidem tartrate) 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

9.3 Dependence

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 U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in 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. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or any other hypnotic.

10 OVERDOSAGE

10.1 Signs and symptoms

In postmarketing experience of overdose with zolpidem 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

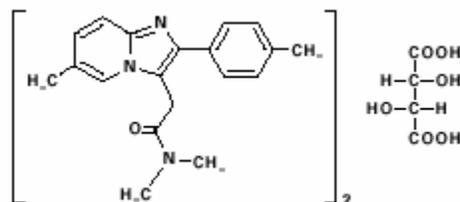
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). 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.

Poison control center: 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 non-benzodiazepine hypnotic 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

Subunit modulation of the GABA_A receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the GABA_A receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.

While zolpidem 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 omega receptor subtypes, zolpidem *in vitro* binds the (ω_1) receptor preferentially with a high affinity ratio of the alpha₁/alpha₅ subunits. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (parsreticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (ω_1) 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 at hypnotic doses.

12.3 Pharmacokinetics

The pharmacokinetic profile of Ambien is characterized by rapid absorption from the GI 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 volunteers 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 2.2hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, Ambien should not be administered with or immediately after a meal.

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.

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 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 normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency [*see Warnings and Precautions (5) and Dosage and Administration (2)*].

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 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. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr);

after repeated dosing T_{\max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Ambien (zolpidem tartrate) pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Postulated relationship between elimination rate of hypnotics and their profile of common untoward effects: The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and be associated with impairment of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carryover effects related to excessive sedation or CNS depression should be minimal or absent. Ambien has a short half-life and no active metabolites. During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (ie, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with Ambien.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10 mg human dose on a mg/kg or mg/m² basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10 mg human dose on a mg/kg or mg/m² basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human

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

Impairment of fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m². No effects on any other fertility parameters were noted.

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 (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; 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 (10 and 15 mg) 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. Zolpidem 15 mg was superior to placebo on a subjective measure of total sleep latency for the first 3 weeks, on a subjective measure of total sleep time for the first week, and on number of awakenings and sleep quality for the first 2 weeks.

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 volunteers. 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), ie, 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

16.1 How Supplied

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:

<u>NDC Number</u>	<u>Size</u>
0024-5401-31	bottle of 100
0024-5401-34	carton of 100 unit dose
0024-5401-50	bottle of 500

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:

<u>NDC Number</u>	<u>Size</u>
0024-5421-31	bottle of 100
0024-5421-34	carton of 100 unit dose
0024-5421-50	bottle of 500

16.2 Storage and handling

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

17 PATIENT COUNSELING INFORMATION

See Medication Guide. Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics and should counsel them in its appropriate use.

17.1 Information for the Physician

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since “sleep-driving” can be dangerous. This behavior is more likely to occur when Ambien is taken with alcohol or other central nervous system depressants [*see Warnings (5.3)*]. 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.

Patients should be instructed NOT to take Ambien or other sedative-hypnotics when drinking alcohol. In addition, patients should be advised to report all concomitant medications to the prescriber. Patients should be counseled to take Ambien right before they get in bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Patients should be instructed to report events such as “sleep-driving” and other complex behaviors immediately to the prescriber.

17.2 Medication Guide

A patient Medication Guide is available for Ambien which discusses “sleep-driving” as well as other sedative-hypnotic related issues. The prescriber or healthcare professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss contents of the Medication Guide and obtain answers to any questions they may have. The Medication Guide is printed at the end of this document.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Revised October 2007

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

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 doctor about your medical condition or treatment.

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

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 doctor right away if you find out that you have done any of the above activities after taking AMBIEN.

Important:

1. Take AMBIEN exactly as prescribed

- Do not take more AMBIEN than prescribed.
- Take AMBIEN right before you get in bed, not sooner.

2. Do not take AMBIEN if you:

- drink alcohol
 - take other medicines that can make you sleepy. Talk to your doctor about all of your medicines. Your doctor will tell you if you can take AMBIEN with your other medicines.
 - cannot get a full night's 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. Symptoms of insomnia include:

- trouble falling asleep

AMBIEN is not for children.

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 doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take AMBIEN?

Do not take AMBIEN if you are allergic to anything in it. See the end of this Medication Guide for a complete list of ingredients in AMBIEN.

AMBIEN may not be right for you. Before starting AMBIEN, tell your doctor 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, or breastfeeding

Tell your doctor 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.**

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

How should I take AMBIEN?

- Take AMBIEN exactly as prescribed. Do not take more AMBIEN than prescribed for you.
- **Take AMBIEN right before you get into bed.**
- **Do not take AMBIEN unless you are able to stay in bed a full night (7-8 hours) before being active again.**
- For faster sleep onset, AMBIEN should NOT be taken with or immediately after a meal.

- Call your doctor 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, call your doctor or poison control center right away, or get emergency treatment.

What are the possible side effects of AMBIEN?

Possible serious side effects of AMBIEN include:

- **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, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN.

Call your doctor 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
- “drugged feelings”
- You may still feel drowsy the next day after taking AMBIEN. **Do not drive or do other dangerous activities after taking AMBIEN until you feel fully awake.**

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, and stomach area pain.

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

How should I store AMBIEN?

- Store AMBIEN at room temperature, 68° to 77°F (20° to 25° C).
- **Keep AMBIEN and all medicines out of reach of children.**

General Information about 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 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. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AMBIEN that is written for healthcare professionals. For more information about AMBIEN, 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.

Rx Only

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

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

October 2007

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019908Orig1s025

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Sent to sanofi 6/26/07 re: NDAs 19908 and 21774

Good Morning Daryl and Sarah:

Attached are the revised versions of the Med Guide. Our Division of Surveillance Research Communication and Support has re-written the MG. The MG is standardized for all sponsors.

We ask that you implement the MG asap. Submit your MG as a PAS no later than 45 days of receipt of this message.

Any questions,
Pls call me. Thanks,
Cathleen



AMBIEN MG AMBIEN CR MG
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*Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*

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

/s/

Cathleen Michaloski
8/29/2007 08:55:42 AM
CSO

Cathleen Michaloski
8/29/2007 08:58:59 AM
CSO

Sent by email 8/22/07

Please see responses below. We realize that you have submitted your MGs. Sorry for the delay in getting back to you.
Cathleen

*Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*

From: Colleen.Irish@sanofi-aventis.com [mailto:Colleen.Irish@sanofi-aventis.com]
Sent: Thursday, July 26, 2007 9:08 AM
To: Michaloski, Cathleen
Subject: Medication guides for Ambien (19-908) & Ambien CR (21-774)

Dear Cathleen,

Upon reviewing the Medication Guides for Ambien & Ambien CR you presented to us via email on June 26, 2007, we have a question and some concerns/proposals. In an effort to meet the 45 day timeline, we are sending this via e-mail only and hope for a quick reply.

Questions:

1. The box around the controlled substance schedule information could be mistaken to be a "Black Box" warning for a drug that does not have a boxed warning which may cause confusion for consumers that are becoming increasingly aware of the concept of a "Black Box". Are there other format options to provide the prominence desired without using a box?

We do not think that the current presentation will be confused with a "Black box " warning by consumers. We do not have other format options to suggest.

2. "Mental illness" and "lung disease" in the section entitled "**AMBIEN CR may not be right for you**" are broad terms that each describe a collection of disease states. "Mental illness" and "lung disease" are mentioned in the product specific portion of the Medication Guide which must reference the approved professional label.

We feel that the term "lung disease" is too broad and includes conditions that we don't have product specific data to support. More specifically, in our original proposed MG we used the term breathing difficulty to address this concern. We propose changing it to be consistent with the current Package Insert and to say "have difficulty breathing"

Similarly the term "mental illness" is a broad term and includes conditions that may not necessarily warrant a caution when taking a sedative hypnotic, or that we have data to support in our professional package insert. We propose to remove the term "mental illness" and revise the line to read " ... have a history of depression or suicidal thoughts" to be consistent with the current package insert.

While we agree that lung disease and mental illness are broad terms, they are terms that consumers are likely to use and recognize. The Medication Guide does not state that the medication should not be used by these persons but rather encourages the consumer to discuss his/her medical history with the prescriber.

The last question I have is once we submit the Prior Approval Supplement for the MG, what is the time frame for receiving approval?

Within 3 months if no area of disagreement.

Thank you in advance for your consideration of these questions. If you have any concern, please call me at 908-981-7824.

Sincerely,
Colleen

Colleen T. Irish, Manager
U.S. Regulatory Affairs Marketed Products
Phone: 908-981-7479
Fax: 908-635-5840

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/s/

Cathleen Michaloski
8/22/2007 01:39:27 PM
CSO

Cathleen Michaloski
8/22/2007 01:52:14 PM
CSO