Ambien (zolpidem tartrate) tablets C-IV

Initial U.S. Approval: 1992

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.

AMBEN, 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)

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 (2) 4/2013

 WLDOASAGE 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. (2.2)

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)

Known hypersensitivity to zolpidem (4)

CONTRAINDICATIONS

CNS depressant effects: Impairs alertness and motor coordination. Instruct patients on correct use. (5.1)

ADVERSE REACTIONS

Most commonly observed adverse reactions were:

• 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 1-800-533-1610 or FDA at 1-800-FDA-1086, 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 FDA-approved Medication Guide

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS

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
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, can have 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)].

5.2 Need to Evaluate for Co-morbid Diagnoses
Because sleep disturbances may be the presenting manifestation of a physical or psychiatric disorder, symptom 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 medical 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 suggested 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., aggressive ness 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 in < 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) have been reported in patients treated with Ambien (see Warnings and Precautions (5.3)). Some patients have had complete amnesia for the episodes. Some patients have required medical therapy in the emergency department. If sleep-driving occurs, the patient should be accompanied by a responsible adult until the patient can safely drive.

Cases of sleep-related eating disorders, including pica and sleep-related sexual behavior, have been reported. Moreover, patients may have discrete behavioral changes during sleep which seem out of character and which may include sexual, aggressive or other socially inappropriate behaviors. 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)].

5.5 Use in Patients with Depression
Abnormal thinking and behavior changes have been reported in 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 lower oxygen saturation and increase in the percent of time with 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 doses of 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 1,953 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 (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=65) were associated with impaired concentration, or agitation, or agranulocytosis, or macrolide; 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 (5%).

Adverse reactions observed at an incidence of ≥ 1% in controlled trials: The following tables enumerate treatment-emergent adverse reactions frequencies that were observed at an incidence equal to 1% or greater in any 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 different set of conditions. Adverse events which disrupt sleep or reduce 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.

<table>
<thead>
<tr>
<th>Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights (Percentage of patients reporting)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body System/Adverse Event</strong></td>
</tr>
<tr>
<td>Central and Peripheral Nervous System</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Drowsiness</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Gastrointestinal System</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td><em>Reactions reported by at least 1% of patients treated with Ambien and at a greater frequency than placebo.</em></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 35 Nights (Percentage of patients reporting)</th>
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</thead>
<tbody>
<tr>
<td><strong>Body System/Adverse Event</strong></td>
</tr>
<tr>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>Dry mouth</td>
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<tr>
<td>Body as a Whole</td>
</tr>
<tr>
<td>Allergy</td>
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<tr>
<td>Back Pain</td>
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<tr>
<td>Influence-like symptoms</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Cardiovascular System</td>
</tr>
<tr>
<td>Palpitation</td>
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<tr>
<td>Central and Peripheral Nervous System</td>
</tr>
<tr>
<td>Drowsiness</td>
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<tr>
<td>Dizziness</td>
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</tbody>
</table>
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 tabular 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 increasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 patients; 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, pailor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tachycardia.

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: atrial fibrillation, arrhythmia, artery, 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, dysautonomia, emotional lability, hallucination, hypothetazia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tachycardia.

Dermatologic system: Frequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria. Special senses: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, eyelids, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia, taste perversion.

Gastrointestinal system: Frequent: ataxia, confusion, euphoria, headache, insomnia, vertigo. Infrequent: increased sweating, pailor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tachycardia.

Skin and Appendages: Infrequent: rash. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

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


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 25% 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 CYP3A4 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 abstinence 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 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/m2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day increased embryofetal death and incomplete fetal skull 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/m2 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/m2 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) on an oral solution of zolpidem tartrate dose of 0.25 mg/kg/day 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. 15.6%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received placebo and 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).
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)].

10.2 Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage. Dizziness 3% 0%

12.3 Pharmacokinetics

The pharmacokinetic profile of Ambien is characterized by rapid absorption from the gastrointestinal tract and a short elimination half-life (T1/2) in healthy subjects. A single-dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (Cmax) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (Tmax) of 1.6 hours for both. The peak concentration in cirrhotic patients (n=11) was significantly lower (48%) and T1/2 was significantly increased (2.0 to 1.0 hours) compared to healthy subjects. The mean elimination half-life (T1/2) in cirrhotic patients was 121 (range: 58 to 272) ng/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 8 patients with chronic hepatic insufficiency were compared to healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean Cmax and AUC were found to be two times (256 vs. 384 ng/mL) and five times (595 vs. 1562 ng/mL), respectively, as compared to healthy subjects (n=11).

13.2 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 binds to the BZ receptor preferentially with a high affinity ratio of the α1/β2 subunits. This selective binding of zolpidem on the BZ 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 hypnosedative doses.

Zolpidem is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 268.3.

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.

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 binds to the BZ receptor preferentially with a high affinity ratio of the α1/β2 subunits. This selective binding of zolpidem on the BZ 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 hypnosedative doses.
A single-dose interaction study with zolpidem tartrate 10 mg and ritamipin 600 mg at steady-state levels in female subjects showed significant reductions in the AUC (73%), Cmax (-58%), and T1/2 (-56%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Ritalpin, 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 ketocazone, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonging 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 ketocazone 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 male and female rats for 2 years at oral doses of 0.5, 1, 3, 10, 30, and 100 mg/kg daily. 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/m2 basis. In rats, these doses are approximately 5, 20, and 100 times the MRHD on a mg/m2 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 toxicity 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 preovulatory intervals at the highest dose tested. The no-effect dose for these findings is approximately 24 times the MRHD on a mg/m2 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 years) 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. 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 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 was not 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 adults who are 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 (30 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:

NDC Number | Size |
--- | --- |
0024-5401-31 | bottle of 100 |
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:

NDC Number | Size |
--- | --- |
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.

17.1 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 present despite feeling fully awake.

17.2 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.

17.3 Sleep-driving and Other Complex Behaviors

Inform 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.

17.4 Suicide

Tell patients to immediately report any suicidal thoughts.

17.5 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 bedtime.

17.6 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”.

17.7 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.

17.8 MEDICATION GUIDE

AMBEN® (am-bé-en) (zolpidem tartrate)

Tablets C-IV

Tablets are caplets and were yellow, film coated, with AMB 5 and 10 debossed on one side and 5401 or 5421 on the other.

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.

AMBEN 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?
AMIEN 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.

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?
AMIEN may not be right for you. Before starting AMBIEN, tell your healthcare provider about all of your health conditions, including:
- 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
- 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?
AMIEN 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?”
- 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
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