AMBIEN (zolpidem tartrate) tablets, for oral use, 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.

AMBIEN® (zolpidem tartrate) tablets, for oral use, C-IV

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Dosage Forms and Strengths

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

Contraindications

• Known hypersensitivity to zolpidem (4)

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10/2014

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New full prescribing information: See 17 for Patient Counseling Information and FDA-approved Medication Guide

Revised: 10/2014
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)].

5.8 Severe Injuries
Zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries. Severe injuries such as hip fractures and intracranial hemorrhage have been reported.

6. ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling:
- CNS-depressant effects and next-day impairment [see Warnings and Precautions (5.1)]
- Serious anaphylactic and anaphylactoid reactions [see Warnings and Precautions (5.3)]
- Abnormal thinking and behavior changes, and complex behaviors [see Warnings and Precautions (5.4)]
- Withdrawal effects [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience
Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%). Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

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

Most commonly observed adverse reactions in controlled trials: During short-term treatment (up to 10 nights) with AMBIEN at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (29 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 drug-induced feelings (3%).

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 among patients with insomnia who received zolpidem tablets 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 the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

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

### Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zolpidem (10 mg)</th>
<th>Placebo (N=473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Diaphores</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

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

The following table was derived from results of three placebo-controlled long-term efficacy trials involving AMBIEN (zolpidem tartrate). These trials involved patients with chronic insomnia who were treated for up to 39 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 Reactions in Placebo-Controlled Clinical Trials Lasting up to 35 Nights (Percentage of patients reporting)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zolpidem (10 mg)</th>
<th>Placebo (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic Nervous System</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

Reactions reported by at least 1% of patients treated with AMBIEN and at a greater frequency than placebo.
Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials Lasting up to 35 Nights (Percentage of Patients Reporting) (continued)

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Zolpidem (≤10 mg) (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and Peripheral Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Drugged feeling</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Amnesia</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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

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

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited at least once 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 systems 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 subjects; rare events are those occurring in less than 1/1,000 subjects.

Gastrointestinal System: Infrequent: increased salivation, altered taste, nausea, vomiting, diarrhea, constipation, abdominal pain, constipation, rash.

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

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

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

7 Drug Interactions

7.1 CNS-Active Drugs

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

Imipramine, Chlorpromazine

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

Haloperidol

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

Alcohol

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

Sertraline

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

Fluoxetine

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

7.2 Drugs That Affect Drug Metabolism via Cytochrome P450

Zolpidem is metabolized by the cytochrome P450 enzymes CYP2C19 and CYP3A4. The majority of patients known to inhibit CYP2C19 may increase exposure to zolpidem. The effect of other drugs on the metabolism of zolpidem is unknown. 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 morphine 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 at doses greater than the AMBIEN maximum recommended human dose (MRHD) of 10 mg/day (approximately 8 mg/day zolpidem base); however, teratogenicity was not observed. When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 5 times the MRHD on a mg/kg 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 skeletal ossification occurred at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/kg 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/kg basis.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

In an 8-week study, in pediatric patients (aged 6–17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) an oral solution of zolpidem tartrate dosage at 0.25 mg/kg 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. 15.1%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [see Warnings and Precautions (5.4)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

8.5 Geriatric Use

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥ 60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).
and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see Warnings and Precautions (5.1)].

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs classified by the U.S. Food and Drug Administration as sedative/hypnotic or anxiolytic agents. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem in vitro binds the B2 receptor preferentially with a high affinity ratio of the cerebral cortex over the spinal cord [see Warnings and Precautions (5.1)]. This selective binding of zolpidem on the B2 receptor is not absolutely unique and can explain the relative insensitivity of the midazolam 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 gastrointestinal tract and a short elimination half-life (T1/2) in healthy subjects. In a single-dose crossover study in 45 healthy subjects administered 5 mg 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 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 92.0 ± 0.3% and remained constant, independent of concentration between 40 and 790 mg per tablet. Zolpidem did not accumulate in young subjects following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks. A food-effect study in 20 healthy male subjects compared the pharmacokinetics of AMBIEN 10 mg when administered with a standardized meal and following a 10 mg zolpidem tartrate tablet after 20 minutes at a meal. Results demonstrated that with food, mean AUC and Cmax were decreased by 15% and 25%, respectively, while mean Tmax was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, AMBIEN should not be administered with or immediately after a meal.

Special Populations (Elderly): In the elderly, the dose for AMBIEN should be 5 mg [see Warnings and Precautions (5) and Dosage and Administration (2)]. This recommendation is based on several in studies in which the mean Cmax, T1/2, and AUC were significantly increased when compared to results in young adults (20 to 40 years). In one study of eight elderly subjects (≥ 70 years), the means for Cmax and AUC significantly increased by 50% (255 vs. 384 ng/mL), 32% (2.2 vs. 2.9 hr), and 94% (955 vs. 1,562 ng·hr/mL), respectively, as compared to the data from a 20 mg oral dose (40 mg oral dose). AMBIEN did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 21 days.

Hepatic Impairment: The pharmacokinetics of AMBIEN in eight patients with chronic hepatic insufficiency were compared to those of healthy subjects. Patients received a single 20 mg oral zolpidem tartrate dose, and Cmax, AUC, and Tmax 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. Tmax did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency [see Dosage and Administration (2.2)].

Renal Impairment: The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (creatinine clearance of ≤ 10 mL/min) and 10 healthy male volunteers receiving a single 20 mg oral zolpidem tartrate dose. Zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for Cmax, Tmax, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of zolpidem and metabolites was observed after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

Drug Interactions

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

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not preclude the existence of an effect following chronic administration. An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see Warnings and Precautions (5.1)].

Following five consecutive nightly doses at bed time of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem Cmax was significantly higher (43%) and Tmax was significantly decreased (-35%). Pharmacokinetics of zolpidem were not adversely affected by sertraline.
A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (75%), Cmax (57%), and T1/2 (36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketocanozole, 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 prolonged the elimination half-life (30%) along with an increase in the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when concomitant ketocanozole 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 prothrombin time when given with warfarin in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 16, and 80 mg/kg. In mice, these doses are approximately 2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/dy (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/d) to rats prior to and during mating, and continuing in females postpartum day 25, resulted in irregular estrus cycles, precocial 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, percentage of time in REM sleep, and number of awakenings. Normal elderly adults (mean age 68) experiencing transient insomnia (n = 35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

14.2 Chronic Insomnia

Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n = 75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied. Adult outpatients (n=141) with chronic insomnia were also evaluated in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep efficiency for the first treatment week. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with AMBIEN.

14.3 Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs

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

Memory impairment: Controlled studies in adults utilizing objective measures of memory yielded no evidence of memory impairment following 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 the evening prior (90 minutes post-dose), i.e., these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of AMBIEN, predominantly at doses above 10 mg.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>0024-5401-31</td>
<td>bottle of 100</td>
<td>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:</td>
</tr>
</tbody>
</table>
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?
AMBEN may not be right for you. Before starting AMBIEN, tell your healthcare provider about all of your health conditions, including if you:
- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. It is not known if AMBIEN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. AMBIEN can pass into your breast milk. It is not known if AMBIEN will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN.

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.
Medicines can interact with each other, sometimes causing serious side effects. Do not take AMBIEN with other medicines that can make you sleepy unless your healthcare provider tells you to.

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

How should I take AMBIEN?

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

What are the possible side effects of AMBIEN?
AMBEN may cause serious side effects, including:
- getting out of bed while not being fully awake and do an activity that you do not know you are doing. See “What is the most important information I should know about AMBIEN?”
- abnormal thoughts and behavior. Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- memory loss
- anxiety
- severe allergic reactions. Symptoms include swelling of the tongue or throat, and trouble breathing. Get emergency medical help if you get these symptoms after taking AMBIEN.
- falls, which may lead to severe injuries

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
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