WARNINGS AND PRECAUTIONS

- CNS-Depressant Effects: Impairs alertness and motor coordination including risk of morning impairment. Risk increases with dose and use with other CNS depressants and alcohol. Instruct patients on correct use. (5.2)
- Need to Evaluate for Comorbid Diagnoses: Re-evaluate if insomnia persists after 7 to 10 days of use. (5.3)
- Severe Anaphylactic/Anaphylactoid Reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.4)
- Abnormal Thinking and Behavioral Changes: Changes including decreased inhibition, bizarre behavior, agitation, and depersonalization have been reported. Immediately evaluate any new onset behavioral changes. (5.5)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.6)
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.7)
- Hepatic Impairment: Avoid AMBIEN use in patients with severe hepatic impairment. (5.8)
- Withdrawal Effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.9, 5.10)

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 1-800-632-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.2, 7.1)
- Chlorpromazine: Increased sedation observed (7.1)
- CYP3A4 inducers (rifampin or St. John's wort): Combination use may decrease effect (7.2)
- Ketoconazole: Combination use may increase effect (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause respiratory depression and sedation in neonates with exposure late in the third trimester. (8.1)
- Lactation: A lactating woman may pump and discard breast milk during treatment and for 23 hours after AMBIEN administration. (8.2)
- Pediatric use: Safety and effectiveness not established. Do not rechallenge if such reactions occur. (5.4)
- Other psychiatric and/or nervous system adverse reactions were observed frequently in children aged 3 to 12 years of age and pediatric patients with Attention-Deficit/Hyperactivity Disorder. (5.5, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2019

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**1 INDICATIONS AND USAGE**

AMBIEN (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulty initiating sleep or maintaining sleep, or early morning wakening, when initiated alone, or in combination with behavioral interventions (see Contraindications [4]). 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 Dose 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 alertness [see Warnings and Precautions (5.2)]. The total dose of AMBIEN should not exceed 10 mg once daily immediately before bedtime. AMBIEN should be taken as a single dose and should not be readministered during the same night.

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. The recommended dose of AMBIEN in these patients is 5 mg once daily immediately before bedtime [see Warnings and Precautions (5.2)]. Patients with liver disease may require a dose adjustment because of impaired drug clearance [see Drug Interactions (7.2), Use with CNS Depressants (8.7)]. Patients with liver disease may be more sensitive to the effects of zolpidem. The recommended dose of AMBIEN in patients 65 years and older is 5 mg once daily immediately before bedtime. AMBIEN should be used with caution in patients receiving medications associated with hepatic enzyme inhibition or induction due to the risk of zolpidem accumulation. Use the lowest effective dose for 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 [see Warnings and Precautions (5.2)]. The total dose of AMBIEN should not exceed 10 mg once daily immediately before bedtime. AMBIEN should be taken as a single dose and should not be readministered during the same night. The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Complex Sleep Behaviors**

Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following the first or any subsequent use of AMBIEN. Patients can be warned against driving and other activities requiring complete mental alertness if AMBIEN is taken in these circumstances [see Drug Interactions (7.1)]. Discontinue AMBIEN immediately if a patient experiences a complex sleep behavior [see Contraindications (4)].

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

AMBIEN, like other sedative-hypnotic drugs, has CNS-depressant effects. Coadminstration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression [see Drug Interactions (7.1)]. Dosage adjustments of AMBIEN and of other concomitant CNS depressants may be necessary when AMBIEN is administered with such agents because of the potentially additive effects. The use of AMBIEN with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended [see Dosage and Administration (2.3)].

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

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, sleepiness, blurred/double vision, reduced alertness, and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7–8 hours) is recommended. Because AMBIEN can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk for accidents than placebo-treated patients when treated with AMBIEN 10 mg at bedtime 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 treatment. The risk of next-day psychomotor impairment, including impaired driving, is increased if AMBIEN is taken with less than a full night of sleep (7 to 8 hours); if a higher than the recommended dose is taken; if coadministered with other CNS depressants or alcohol; or if coadministered with other drugs that increase the blood levels of zolpidem. Patients should be warned against driving and other activities requiring complete mental alertness if AMBIEN is taken in these circumstances [see Drug Interactions and Administration (2), Clinical Studies (14.3)].

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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 investigations 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.

Table 1: Incidences of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Zolpidem (&lt;10 mg) (N=683)</th>
<th>Placebo (N=473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and Peripheral Nervous System</td>
<td></td>
<td></td>
</tr>
<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></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</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.

Table 2: Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials Lasting up to 35 Nights (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Zolpidem (&lt;10 mg) (N=152)</th>
<th>Placebo (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3</td>
<td>2</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></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>2</td>
<td>-</td>
</tr>
<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>Anemia</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>Sinusitis</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.
8.1 Pregnancy

Risk Summary

Neonates born to mothers using zolpidem late in the third trimester of pregnancy have been reported to experience symptoms of respiratory depression and sedation [see Clinical Considerations and Data]. Published data on the use of zolpidem during pregnancy have not reported a clear association with zolpidem and major birth defects [see Data]. Oral administration of zolpidem to pregnant rabbits and rats did not indicate a risk for adverse effects on fetal development at clinically relevant doses [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage for clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Zolpidem crosses the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to AMBIEN during pregnancy and labor for signs of excess sedation, hypotonia, and respiratory depression and manage accordingly.

Data

Human data from observational studies, birth registries, and case reports on the use of zolpidem during pregnancy do not report a clear association with zolpidem and major birth defects.

There are limited postmarketing reports of severe to moderate cases of respiratory depression that occurred after birth in neonates whose mothers had taken zolpidem during pregnancy. These cases required artificial ventilation or intratracheal intubation. The majority of neonates recovered within hours to a few weeks after birth once treated.

Zolpidem has been shown to cross the placenta. Animal data

Oral administration of zolpidem to pregnant rats during the period of organogenesis at 4, 20, and 100 mg base/kg/day, which are approximately 5, 25, and 120 times the maximum recommended human dose (MRHD) of 10 mg (8 mg zolpidem base) based on mg/m² body surface area, caused delayed fetal development (incomplete fetal skeletal ossification) at maternally toxic (ataxia) doses 25 and 120 times the MRHD based on mg/m² body surface area.

Oral administration of zolpidem to pregnant rabbits during the period of organogenesis at 1, 4, and 16 mg base/kg/day, which are approximately 5, 20, and 120 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m² body surface area caused embryofetal death and delayed fetal development (incomplete fetal skeletal ossification) at a maternally toxic (decreased body weight gain) dose 40 times the MRHD based on mg/m² body surface area.

Oral administration of zolpidem to pregnant rats from day 15 of gestation through lactation at 4, 20, and 100 mg base/kg/day, which are approximately 5, 25, and 120 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m² body surface area, delayed offspring growth and decreased survival at doses 25 and 120 times, respectively, the MRHD based on mg/m² body surface area.

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of zolpidem in human milk. There are reports of excess sedation in infants exposed to zolpidem through breastmilk [see Clinical Considerations]. There is no information on the effects of zolpidem on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AMBIEN and any potential adverse effects on the breastfed infant from AMBIEN or from the underlying maternal condition.

Clinical Considerations

Infants exposed to AMBIEN through breastmilk should be monitored for excess sedation, hypotonia, and respiratory depression. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 23 hours (approximately 5 elimination half-lives) after AMBIEN administration in order to minimize drug exposure to a breast fed infant.

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 (ages 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [see Warnings and Precautions (5.5)]. 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 ≥65 years of age. A total of 24/1695 (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 cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see Warnings and Precautions (5.2)].

8.6 Gender Difference in Pharmacokinetics

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

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

8.7 Hepatic Impairment

The recommended dose of AMBIEN in patients with mild to moderate hepatic impairment is 5 mg only during the immediate before bedtime. Avoid AMBIEN use in patients with severe hepatic impairment as it may contribute to encephalopathy [see Dosage and Administration (2.2), Warnings and Precautions (5.8), Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation where 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. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation where 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.

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

9.3 Dependence

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

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events, which are considered to meet the DI or ADR criteria, have been reported. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Postmarketing reports of abuse, dependence and withdrawal have been reviewed.

10 OVERDOSAGE

10.1 Signs and Symptoms

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

10.2 Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem’s sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated where appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdose, even if excitation occurs. The value of dialysis in the treatment of overdose
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 contains the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colored, and polyethylene 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem is a nonbenzodiazepine receptor positive modulator of the imidazopyridine class. AMBIEN is available in 5 mg and 10 mg strength tablets for oral administration.

12.2 Pharmacodynamics

Zolpidem binds to GABA A receptors with greater affinity for α1 subunit relative to α2 and α3 subunit containing receptors. Zolpidem has no appreciable binding affinity for κ6 subunit containing GABA A receptors. This binding profile may explain the relative absence of myorelaxant effects in animal studies. Zolpidem binding affinity for dopaminergic D2, serotonin 5HT1A, adrenergic, histaminergic or muscarinic receptors.

12.3 Pharmacokinetics

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

In a single-dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C max) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL respectively, occurring at a mean time (T max) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is considered 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 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

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

Special Populations

In the elderly, the dose for AMBIEN should be 5 mg [see Warnings and Precautions (5)]. Dosage and Administration (2)]. This recommendation is based on several studies in which the mean C max, T max 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 max and AUC significantly increased by 50% (550 vs 384 ng/mL), 92% (2.2 vs 2.9 hr), and 64% (555 vs 1,562 ng/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20 mg oral zolpidem tartrate tablet for 2 weeks.

Hepatic impairment

The pharmacokinetics of AMBIEN in eight patients with chronic hepatic insufficiency was compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean C max and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng/mL) higher, respectively, in hepatologically compromised patients. T max did not change. The mean half-life in cirrhotic patients of 9.8 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) [see Dosage and Administration (2.2), Warnings and Precautions (5.8), Use in Specific Populations (8.7)].

Renal impairment

The pharmacokinetics of zolpidem tartrate was studied in 11 patients with end-stage renal failure (mean Ccr = 6.5 ± 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 and AUC between the first and last day of drug administration when baseline corticosteroid and diuretic treatments were unchanged. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics was not significantly different in renal impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

Drug Interactions

CNS depressants

Coadministration of zolpidem with other CNS depressants increases the risk of CNS depression [see Warnings and Precautions (5.2)]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Irpiriprazole in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration. An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see Warnings and Precautions (5.2)]. Following five consecutive nights of bedtime oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C max was significantly higher (43%) and T max was significantly decreased (-33%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 200 mg at steady-state levels in middle-aged volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

Drugs that affect drug metabolism via cytochrome P450 Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and larancoze 200 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and larancoze were given at steady state, the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

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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 who did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound Effects

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

Memory Impairment

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

Effects on Sleep Stages

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

15 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

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

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the 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.

Complex Sleep Behaviors

Instruct patients and their families that AMBIEN may cause complex sleep behaviors, including sleep-walking, sleep-driving, preparing and eating food, making phone calls, or having sex while not being fully awake. Serious injuries and death have occurred during complex sleep behaviors. Tell patients to discontinue AMBIEN and notify their healthcare provider immediately if they develop any of these symptoms (see Boxed Warning, Warnings and Precautions (5.1)).

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 be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients (see Warnings and Precautions (5.2)).

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 (see Warnings and Precautions (5.4)).

Suicide

Tell patients to immediately report any suicidal thoughts.

Alcohol and Other Drugs

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

Tolerance, Abuse, and Dependence

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

Administration Instructions

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

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with AMBIEN. Advise patients that use of AMBIEN late in the third trimester may cause respiratory depression and sedation in neonates. Advise mothers who used AMBIEN during the late third trimester of pregnancy to monitor neonates for signs of sleepiness (more than usual), breathing difficulties, or impairs (see Use in Specific Populations (8.1)).

Lactation

Advise breastfeeding mothers using AMBIEN to monitor infants for increased sleepiness, breathing difficulties, or impairs. Instruct breastfeeding mothers to seek immediate medical care if they notice these signs. A lactating woman may consider pumping and discarding breastmilk during treatment and for 23 hours after AMBIEN administration to minimize drug exposure to a breastfed infant (see Use in Specific Populations (8.2)).

MEDICATION GUIDE

AMBIEN® (ām’be –on) (zolpidem tartrate) tablets C-IV

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

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

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

AMBIEN may cause serious side effects, including:
• complex sleep behaviors that have caused serious injury and death. 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 (complex sleep behaviors). The next morning, you may not remember that you did anything during the night. These activities may occur with AMBIEN whether or not you drink alcohol or take other medicines that make you sleepy. Reported activities include:
  o driving a car ("sleep-driving")
  o making and eating food
  o talking on the phone
  o having sex
  o sleep-walking

Stop taking AMBIEN and 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:
• have ever experienced a complex sleep behavior (such as driving a car, making and eating food, talking on the phone, or having sex while not being fully awake) after taking AMBIEN.
• drank alcohol that evening or before bed
• took another medicine to help you sleep

What is AMBIEN?

AMBIEN is a sedative-hypnotic (sleep) medicine. AMBIEN is used in adults for the short-term treatment of a sleep problem called insomnia (trouble falling asleep). AMBIEN is not recommended for use in children under the age of 18 years.

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

Who should not take AMBIEN?

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

Symptoms of a serious allergic reaction to zolpidem can include:
• swelling of your face, lips, and throat that may cause difficulty breathing or swallowing
What should I tell my healthcare provider before taking AMBIEN? AMBIEN may not be right for you. Before starting AMBIEN, tell your healthcare provider about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. Talk to your healthcare provider about the risk to your unborn baby if you take AMBIEN.
- Using AMBIEN in the last trimester of pregnancy may cause breathing difficulties or excess sleepiness in your newborn. Monitor for signs of sleepiness (more than usual), trouble breathing, or limppness in the newborn if AMBIEN is taken late in pregnancy.
- are breastfeeding or plan to breastfeed. AMBIEN passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN.

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

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

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

How should I take AMBIEN?

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

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

What are the possible side effects of AMBIEN?

AMBIEN may cause serious side effects, including:

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

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

The most common side effects of AMBIEN are:

- drowsiness
- dizziness
- diarrhea
- groginess 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 doctor 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, microcrystalline 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.

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A SANOFI COMPANY

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