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

Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Dosage and Administration, Dosage in Adults (2.1) 8/2016
Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.1) 8/2016

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 of treatment. (4)

Dosage and Administration

Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and 2.1 Dosage in Adults

Recommended initial dose is a single dose of 5 mg for women and a single dose of 5 or 10 mg for men, immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening. (2.1)

Geriatric patients and patients with hepatic impairment: Recommended dose is 5 mg for men and women. (2.2)

Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN (2.3)

The effect of AMBIEN may be slowed if taken with or immediately after a meal. (2.4)

Dosage Forms and Strengths

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

Contraindications

Known hypersensitivity to zolpidem (4)

WARNINGS AND PRECAUTIONS

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

• Need to evaluate for co-morbid diagnosis: Reevaluate if insomnia persists after 7 to 10 days of use. (5.2)

• Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)

• Sleep-driving* and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)

• Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.5)

• Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function (5.6)

• Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation (5.7, 9.3)

• Severe Injuries: Drowsiness may lead to fall including severe injuries (5.8)

ADVERSE REACTIONS

Most commonly observed adverse reactions were:

Short-term (< 10 nights): Drowsiness, dizziness, and diarrhea

Long-term (28 – 35 nights): Dizziness and drugged feelings (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1985, 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)

• CYP3A4 inducers (e.g. rifampin): Combination use may decrease effect (7.2)

• CYP3A4 inhibitors (e.g. ketoconazole): Combination use may increase effect (7.2)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Based on animal data, may cause fetal harm (8.1)

• Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder (5.4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide Revised: 08/2016

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of AMBIEN in both of these patient populations is 5 mg once daily immediately before bedtime [see Warnings and Precautions (5.1); Use in Specific Populations (8.5)].

2.3 Use with CNS Depressants

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

2.4 Administration

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

3 DOSAGE FORMS AND STRENGTHS

AMBIEN is available in 5 mg and 10 mg strength tablets for oral administration. Tablets are not scored. AMBIEN 5 mg tablets are capsule-shaped, pink, film coated, with AMB 5 debossed on one side and 54101 on the other. AMBIEN 10 mg tablets are capsule-shaped, white, film coated, with AMB 10 debossed on one side and 5421 on the other.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-Day Impairment

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

The risk of next-day psychomotor impairment, including impaired driving, is increased if AMBIEN is taken with less than a full night of sleep remaining (7 to 8 hours); if a higher than the recommended dose is taken; if co-administered with other CNS depressants or alcohol; or if co-administered 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 Dosages and Administration (2) and 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, dizziness, sleepiness, blurred vision, and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7-8 hours) is recommended.

5.2 Need to Evaluate for Co-morbid Diagnoses

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

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Cases of anaphylactic and anaphylactoid reactions, including anaphylactic shock, have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If an anaphylactic reaction occurs, the drug should be discontinued and appropriate diagnostic and therapeutic measures taken.

5.4 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedative/hypnotics, including AMBIEN. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depression, visual hallucinations to the incidence of side effects in the population studied.

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. Each group of drug trials is conducted under a different set of conditions. These 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 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 three placebo-controlled long-term 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-Emmergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights (Percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System/ Adverse Event</th>
<th>Zolpidem (≤10 mg) (N=161)</th>
<th>Placebo (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and Peripheral Nervous System</td>
<td>Headache</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>Diarrhea</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.*

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

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

<table>
<thead>
<tr>
<th>Body System/ Adverse Event</th>
<th>Zolpidem (16 mg) (N=152)</th>
<th>Placebo (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic Nervous System</td>
<td>Dry mouth</td>
<td>3</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Body as a Whole</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Back Pain</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Influenza-like symptoms</td>
<td>2</td>
</tr>
</tbody>
</table>
Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Zolpidem (≤10 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=152)</td>
<td>(N=161)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Palpitation</td>
<td></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>Dugred feeling</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Amnesia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></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 on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with AMBIEN, they were not necessarily caused by it.

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

Autonomic nervous system: Infrequent: increased sweating, pallor, postural hypotension, syncope.

Cardiovascular system: Infrequent: careabolouris disorders, hypotension, tachycardia.

Central and peripheral nervous system: Infrequent: ataxia, confusion, euphoria, headache, insomnia, vertigo. Infrequent: agitation, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypotension, insomnia, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal swallowing, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dizziness, feeling strange, hypokinesia, hypomania, hypesthesia, inattention, isolated feeling, memory loss, mood swings, nervousness, obsession, panic attacks, paresthesia, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: dyspepsia, hiccup, nausea. Infrequent: anorexia, constipation, diarrhea, flatus, flatulence, gastritis, vomiting. Rare: enteritis, eructation, esophagospasm, gastritis, hemmorhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphopenopa-thy, macrocytic anemia, purpura, thrombosis.

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

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

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesterolemia, hyperlipidemia, increased alkaline phosphatase, increased BUN, perifolliculitis.


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

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

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

Special senses: Frequent: diplopia, eye irritation, eye pain, sciatica, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, paroxysm, photopsia.

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

7. DRUG INTERACTIONS

7.1 CNS-active Drugs

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression.

Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability. [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 alriest. 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)].

Sedatives

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

Flurideline

After multiple doses of zolpidem tartrate and flurideline 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 induce or inhibit CYP3A4 may affect exposure to zolpidem. The effect of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known.

CYP3A4 Inducers
Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of CYP3A4 inducers in combination with zolpidem may decrease the efficacy of zolpidem [see Clinical Pharmacology (12.3)].

CYP3A4 Inhibitors
Ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to and pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when a potent CYP3A4 inhibitor and zolpidem are given together [see Clinical Pharmacology (12.3)].

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 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 fadclity 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/g kilogram body weight); 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 embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/kg basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day for the latter part of pregnancy and throughout lactation did not impair birth weight 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 (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 experiences observed with zolpidem versus placebo and included dizziness (25.5% vs. 15.5%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [see Warnings and Precautions (5.4)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.
8.5 Geriatric Use
A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥ 60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤ 10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

### Adverse Event

<table>
<thead>
<tr>
<th>Zolpidem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>3%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>3%</td>
</tr>
</tbody>
</table>

A total of 30,195 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28,30 (82%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24,195 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18,247 (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)].

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.

### 9. Drug Abuse and Dependence

#### 9.1 Controlled Substance
Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

#### 9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects. Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo. Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse, and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

#### 9.3 Dependence

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

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence and withdrawal have been received.

### 10. OVERDOSAGE

#### 10.1 Signs and Symptoms

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

#### 10.2 Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage. In the elderly, the dose for AMBIEN should be 5 mg regardless of gender.

### 11. DESCRIPTION

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

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

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and benzylalcohol. It has a molecular weight of 764.88. Each AMBIEN tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polyborate 80.

### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a BABA-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 B1/B2 subunits. This selective binding of zolpidem on the B2 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

#### 12.3 Pharmacokinetics

The pharmacokinetic profile of AMBIEN is characterized by rapid absorption from the gastrointestinal tract and a short elimination half-life (T1/2) 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 (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 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 < 0.1% and remained constant, independent of concentration between 40 and 970 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 2 hours after eating and while fasting or 25 minutes after 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.

#### 12.4 Special Populations

Elderly: In the elderly, the dose for AMBIEN should be 5 mg [see Warnings and Precautions (5) and Dosage and Administration (2)]. This recommendation is based on several studies in which the mean Cmax, Tmax and AUC were found to be two times (78 vs. 499 ng/mL) and five times (786 vs. 4,203 ng·hr/mL), higher, respectively, in elderly compared to younger adults (20 to 40 years) following a single 20 mg oral dose of AMBIEN. AMBIEN did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Hepatic Impairment: The pharmacokinetics of AMBIEN in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean Cmax and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (>70 years), the means for Cmax, Tmax 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 younger adults (20 to 40 years) following a single 20 mg oral dose. AMBIEN did not accumulate in markedly impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

#### 12.5 Drug Interactions

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [see Drug Interactions (7)]. When zolpidem tartrate was given to healthy volunteers, it had an additive effect on psychomotor performance.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was observed for Cmax and Tmax. Activity levels 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.

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 indicates that doses may predict the absence of chronic administration. An additive adverse effect on psychomotor performance between alcohol and zolpidem was demonstrated [see Warnings and Precautions (5.1)]. Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sedative hypnotic doses of zolpidem, 10 mg (7 consecutive daily doses, at 7:30 am, in healthy female volunteers), zolpidem Cmax was significantly higher (43%) and T1/2 was significantly decreased (63%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interaction.
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 CYP3A4 may increase exposure to zolpidem. The effect of inhibitors of other P450 isoenzymes on the pharmacokinetics of zolpidem is unknown. A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in AUC of zolpidem. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (73%), Cmax (58%), and T1/2 (36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP1A2 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem (see Drug Interactions (7.2)).

A single-dose interaction study with zolpidem tartrate 5 mg and ketaconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem (50%) 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 (see Drug Interactions (7.2)).

Additionally, fluvoxamine (a strong inhibitor of CYP1A2 and a weak inhibitor of CYP3A4 and CYP2C9) and ciprofloxacin (a strong inhibitor of CYP1A2 and a moderate inhibitor of CYP3A4) are also likely to inhibit zolpidem’s metabolic pathways, potentially leading to an increase in zolpidem exposure. Other Drugs with No Interactions with Zolpidem
A study involving cyclosporine/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 Carcinogenicity, Mutagenesis, Impairment of Fertility
Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg. In mice, these doses are approximately 2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/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 microsome) 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 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) 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-III-R). 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 also superior to placebo on number of awakenings at both doses tested at both weeks tested.

Adult patients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with AMBIEN.

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

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of AMBIEN (zolpidem tartrate). There was subjective evidence of rebound 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, white, film coated, with AMB 10 debossed on one side and 5421 on the other and supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0024-5451-31</td>
<td>bottle of 100</td>
</tr>
<tr>
<td>0024-5421-31</td>
<td>bottle of 100</td>
</tr>
<tr>
<td>0024-5451-50</td>
<td>bottle of 500</td>
</tr>
</tbody>
</table>

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.

ONSET DEPRESSANT EFFECTS AND NEXT-DAY IMPAIRMENT
Tell patients that AMBIEN has the potential to cause next-day impairment, and that this risk 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. Informed patients that impairment can be present despite feeling fully awake.

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

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

Suicide
Tell patients to immediately report any suicidal thoughts.

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

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

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

MEDICATION GUIDE

AMBIEN® (‘amb-é-bén’) (zolpidem tartrate)
Tablets C-IV
Read the Medication Guide that comes with AMBIEN before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AMBIEN?
- Do not take more AMBIEN than prescribed.
- Do not take AMBIEN unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.
- Take AMBIEN right before you get in bed, not sooner.

AMBIEN may cause serious side effects, including:
- After taking AMBIEN, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with AMBIEN. Reported activities include:
  - Driving a car ("sleep-driving")
  - Making and eating food
  - Talking on the phone
  - Having sex
  - Sleep-walking
Call your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN.

Do not take AMBIEN if you:
- drank alcohol that evening or before bed
- took another medicine to help you sleep

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

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

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

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

Symptoms of a serious allergic reaction to zolpidem can include:
- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

What should I tell my healthcare provider before taking AMBIEN?
AMBIEN may not be right for you. Before starting AMBIEN, tell your healthcare provider about all of your health conditions, including if you:
- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. It is not known if AMBIEN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. AMBIEN can pass into your breast milk. It is not known if AMBIEN will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN.

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

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

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

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

ZOL-FPLR-SL-AUG16 Rx Only

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Bridgewater, NJ 08807
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October 2014

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