AMBEN® (zolpidem tartrate) tablets, for oral use, C-IV
Initial U.S. Approval: 1992

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN.

AMBEN®, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. (1)

Dosage and Administration, Dosage in Adults (2.1) 08/2016
Dosage and Administration, Special Populations (2.2) 12/2016
Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.1) 08/2016
Warnings and Precautions, Precipitation of Hepatic Encephalopathy (5.7) 12/2016

INDICATIONS AND USAGE
AMBEN, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. (1)

Dosage and Administration
- Use the lowest dose effective for the patient and must not exceed a total of 10 mg daily (2.1)
- 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 mild to moderate 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 and Next-Day Impairment: Impairs alertness and motor coordination. Instruct patients on correct use. (5.1)

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-1088, or http://www.fda.gov/medwatch

DRUG INTERACTIONS

CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.1, 7.1)
Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
Chlorpromazine: Impaired alertness and psychomotor performance 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: 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: 03/2017

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*Sections or subsections omitted from the full prescribing information are not listed
AMBIEN (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. AMBIEN has been shown to decrease sleep latency for up to 35 days in controlled clinical studies [see Clinical Studies (14)]. The clinical trials performed to support the use of AMBIEN were 4-6 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults

The 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 doses may be necessary. The use of the 10 mg dose increase the risk of next-day impairment of driving and other activities that require full alertness [see Warnings and Precautions (5.1)]. The total dose of AMBIEN should not exceed 10 mg once immediately before bedtime. Ambien should be taken as a single dose and should not be readministered during the same nightly treatment cycle.

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 immediately before bedtime [see Warnings and Precautions (5.1), Use in Specific Populations (8.5)].

Patients with mild to moderate hepatic impairment do not clear the drug as rapidly as normal subjects. The clearance of AMBIEN in these patients is 5 mg once immediately before bedtime. Avoid AMBIEN use in patients with severe hepatic impairment as it may contribute to encephalopathy [see Warnings and Precautions (5.7), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

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 use 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 5421 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 adjustment may be necessary when AMBIEN is co-administered with other CNS depressants. The concomitant administration of AMBIEN with other hypnotics should be done with caution, and the risk to the patient and the community, discontinuation of hypnotics should be carefully considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving," patients and caregivers should be advised to not engage in potentially hazardous activities such as operating motor vehicles or machinery until they are reasonably certain that AMBIEN does not continue to impair their performance on these tasks. AMBIEN use should be discontinued if the patient develops any of these behaviors.

5.2 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 depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials of AMBIEN 10 mg taken at bedtime < 1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with AMBIEN 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [see Use in Speciﬁc Populations (8.4)]

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients taking sedative-hypnotic drugs. Although the risk of such behaviors is low, they have the potential for serious injury to the patient and to others [see Warnings and Precautions (5.1)].

Abnormal thinking and behaviors such as "sleep-driving" have occurred with AMBIEN alone at therapeutic doses, the co-administration of AMBIEN with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of AMBIEN at doses exceeding the maximum recommended dose. Stopping hypnotics should be considered prior to abrupt discontinuation of hypnotics for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving," patients and caregivers should be advised to not engage in potentially hazardous activities such as operating motor vehicles or machinery until they are reasonably certain that AMBIEN does not continue to impair their performance on these tasks. AMBIEN use should be discontinued if the patient develops any of these behaviors. Amnesia, anxiety and other neuro-psychiatric symptoms may also occur. It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or as a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral or symptom of concern requires careful and immediate evaluation.

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Severe anaphylactic and anaphylactoid reactions (including anaphylaxis and angioedema) have been observed in patients treated with sedative-hypnotics, including AMBIEN [see Warnings and Precautions (5.3)]. In primarily depressed patients treated with sedative-hypnotics, worsening of depression, suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

5.4 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the potential to depress respiratory drive, precautions should be taken if AMBIEN is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risk of respiratory depression should be considered prior to prescribing AMBIEN in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.5 Precipitation of Hepatic Encephalopathy

Cases of hepatic encephalopathy have been associated with precipitation of hepatic encephalopathy in patients with hepatic insufficiency. In addition, patients with hepatic insufficiency do not clear zolpidem tartrate as rapidly as patients with normal hepatic function. Avoid AMBIEN use in patients with severe hepatic impairment as it may contribute to encephalopathy [see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

5.6 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose discontinuation or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence [see Drug Abuse and Dependence (9.2) and (9.3)].

5.7 Severe Injuries

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

5.7 Severe Injuries

Cases of hepatic encephalopathy have been associated with precipitation of hepatic encephalopathy in patients with hepatic insufficiency. In addition, patients with hepatic insufficiency do not clear zolpidem tartrate as rapidly as patients with normal hepatic function. Avoid AMBIEN use in patients with severe hepatic impairment as it may contribute to encephalopathy [see Dosage and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

5.6 Withdrawal Effects

Withdrawal effects [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation of zolpidem included: drowsiness (0.9%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%). Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were dizziness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.2%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during treatment with zolpidem (n=53) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Most common adverse events in controlled trials: During short-term treatment (up to 10 nights) with AMBIEN at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28...
to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%). Adverse reactions observed at an incidence of ≥ 1% in controlled trials: The following tables enumerate treatment-emergent adverse reactions frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate and at a greater incidence than placebo in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied. The following table was derived from results of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

### Incidence of Treatment-Emergent Adverse Experiences 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)</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.

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-Emergent Adverse Experiences 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 (≤10 mg)</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>4</td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></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>-</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Amnesia</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinalal 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.

### 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 AMBIEN who experienced an event of the type cited 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 among the following definitions: common 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
Inefrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered salvia, flushing, glaucoma, hypotension, impotence, increased salvia, tenesmus.

#### Body as a whole
Frequent: asthenia. Infrequent: edema, falling, fatigue, fever, malaise, myalgia. Rare: anaphylaxis.

#### Hematologic and lymphatic system
Frequent: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

#### Immune system
Inefrequent: infection. Rare: abscess herpes simplex herpes zoster, otitis externa, otitis media.

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

#### Musculoskeletal and nutritional
Inefrequent: hyperglycemia, thirst. Frequent: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, peripheral edema.

#### Nervous system
Frequent: cerebrovascular disorder, hypertension, tachycardia. Rare: anoxia, coma, convulsion, dysphagia, vertigo, weakness, sedation, tinnitus, vertigo.

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

#### Skin and appendages
Inefrequent: pruritus. Rare: acne, bullous eruption, dermatitis, erythema, hyperpigmentation, increased BUN, periorbital edema.

#### Gastrointestinal system
Frequent: abdominal pain, appetite, diarrhea, vomiting, constipation, anorectal disorder, abnormal feeding, diabetes, increased hepatic transaminases. Rare: anorexia, constipation, dysphagia, flatulence, gastrointestinal, vomiting. Rare: enteritis, eructation, eosinophilia, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

#### Urogenital system
Frequent: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

### 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, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance [see Clinical Pharmacology (12.3)].
A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration [see Clinical Pharmacology (12.3)].

*Alcohol*

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

**Sertraline**

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

**Fluoxetine**

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

**7.2 Drugs that Affect Drug Metabolism via Cytochrome P450**

Some compounds known to induce or inhibit CYP3A 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

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of Rifampin in combination with zolpidem may decrease the efficacy of zolpidem and is not recommended [see Clinical Pharmacology (12.3)].

St. John's Wort

Use of St. John's wort, a CYP3A4 inducer, in combination with zolpidem may decrease blood levels of zolpidem and is not recommended.

CYP3A4 Inhibitors

Ketoconazole

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 respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS-depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. AMBIEN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the AMBIEN maximum recommended human dose (MRHD) of 10 mg/day (approximately 8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during 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/m^2^ 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/m^2^ basis. Administration of zolpidem to pregnant rabbits at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m^2^ basis.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

AMBIEN is not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established. In an 8-week study, in pediatric patients (aged 6–17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric impairment of offspring development at doses greater than the AMBIEN maximum recommended human dose (MRHD) of 10 mg/day (approximately 8 mg/day zolpidem base); however, teratogenicity was not observed.

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).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zolpidem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

A total of 30,159 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28,300 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18,24 (75%) who were ≥ 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

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

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 once daily immediately 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 (5.7), 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 larger quantities and with greater frequency than intended, and/or with other psychotropic drugs. AMBIEN is not associated with a potential for the development of a physical dependence 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 delirium and/or convulsions. The onset, intensity, and duration of withdrawal symptoms are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported withdrawal events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependency 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 medical treatment 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, the patient should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage is not known. Up-to-date information on the management of hypnotic drug product overdosage.

11 DESCRIPTION

AMBIEN (zolpidem tartrate) is a gamma-aminobutyric acid (GABA) 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-tolylimidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:

![Zolpidem Structure](image)

Zolpidem tartrate is a white or off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a melt point of 76.4°C.

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 colorants, and polyethylene 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 GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem in vitro binds the BZ receptor preferentially with a high affinity ratio of the \( \alpha_1 \) over \( \alpha_2 \) subunits. This selective binding of zolpidem on the BZ receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of sleep stages (stages 3 and 4) in human studies of zolpidem atarate 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 (T\(_{1/2}\)). This recommendation is based on several studies in which the mean T\(_{max}\) was 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (T\(_{max}\)) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is converted to inactive metabolites that are eliminated primarily by renal excretion. AMBIEN demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 % ± 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 the mean AUC and T\(_{max}\) were decreased by 15% and 25%, respectively, while mean T\(_{max}\) was prolonged by 60% (from 1.4 to 2.2 hrs). The half-life remained unchanged. These results suggest that, for faster sleep onset, AMBIEN should not be administered with or immediately after a meal.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 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/m\(^2\) basis. In rats, these doses are approximately 5, 20, and 100 times the MRHD on a mg/m\(^2\) basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses. However, the relationship of these findings to zolpidem 

14.2 Chronic Insomnia
Normal adults experiencing persistent insomnia (n = 462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n = 35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15, and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

14.2 Chronic Insomnia
Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV). Adult outpatients with chronic insomnia (n = 75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidam 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 week of sleep and for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n = 141) with chronic insomnia were also evaluated in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on all PSG parameters measured for weeks 1, 2, and 3, 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.
MEDICATION GUIDE
AMBIEN® (am-bé-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:

- 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.

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.

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

- NDC Number
- Size
- 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
- Bottle of 100
- Bottle of 500

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).
Inform patients and their families about the benefits and risks of treatment with AMBIEN. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with AMBIEN and with each prescription refill. Review the AMBIEN Medication Guide with every patient prior to initiation of treatment. Instruct patients and caregivers that AMBIEN should be taken only as prescribed.

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.

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

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 at that evening.
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.