WARNING: COMPLEX SLEEP BEHAVIORS
See full prescribing information for complete boxed warning.
Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of AMBIEN CR. Some of these events may result in serious injuries, including death. Discontinue AMBIEN CR immediately if a patient experiences a complex sleep behavior. (4, 5.1)

INDICATIONS AND USAGE
AMBIEN CR, a gamma-aminobutyric acid (GABA) A receptor positive modulator, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

DOSE AND ADMINISTRATION
• Use the lowest dose effective for the patient and must not exceed a total of 12.5 mg daily (2.1)
• Treatment should be as short as possible (2.1)
• Recommended initial dose is a single dose of 6.25 mg for women and a single dose of 6.25 or 12.5 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 6.25 mg for men and women (2.2)
• Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN CR (2.3)
• Tablets to be swallowed whole, not to be crushed, divided or chewed (2.4)
• The effect of AMBIEN CR may be slowed if taken with or immediately after a meal (2.4)

DOSE FORMS AND STRENGTHS
Extended-Release Tablets: 6.25 mg and 12.5 mg. Tablets not scored. (3)

CONTRAINDICATIONS
• Patients who have experienced complex sleep behaviors after taking AMBIEN CR (4)
• Known hypersensitivity to zolpidem (4)

WARNINGS AND PRECAUTIONS
• CNS-Depressant Effects: Impaired alertness and motor coordination, including risk of morning impairment. Risk increases with dose and use with other CNS depressants and alcohol. Caution patients against driving and other activities requiring complete mental alertness the morning after use. Instruct patients on correct use. (5.2)
• Need to Evaluate for Comorbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days of use. (5.3)
• Severe Anaphylactic/Anaphylactoid Reactions: Anaphylactoid reactions have been reported. Do not rechallenge if such reactions occur. (5.4)
• Abnormal Thinking and Behavioral Changes: Changes including decreased inhibition, bizarre behavior, agitation, and depersonalization have been reported. Immediately evaluate any new onset behavioral changes. (5.5)
• Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.6)
• Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.7)
• Hepatic Impairment: Avoid AMBIEN CR use in patients with severe hepatic impairment. (5.8)
• Withdrawal Effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.9, 9.3)

ADVERSE REACTIONS
Most commonly observed adverse reactions (≥10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (6.1)

USE IN SPECIFIC POPULATIONS
• Pregnancy: May cause respiratory depression and sedation in neonates with exposure late in the third trimester. (8.1)
• Lactation: A lactating woman may pump and discard breast milk during treatment and for 23 hours after AMBIEN CR administration. (8.2)
• 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. (5.5, 8.4)

DRUG INTERACTIONS
• CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.2, 7.1)
• Opioids: Concomitant use may increase risk of respiratory depression (5.7, 7.1)
• Imipramine: Decreased alertness 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)
• Ketaconazole: Combination use may increase effect (7.2)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Gender Difference in Pharmacokinetics
8.7 Hepatic Impairment

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence

10 OVERDOSAGE
10.1 Signs and Symptoms
10.2 Recommended Treatment

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Controlled Clinical Trials
14.2 Studies Pertinent to Safety Concerns for Sedative Hypnotic Drugs

16 HOW SUPPLIED/STORAGE AND HANDLING

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1 INDICATIONS AND USAGE
AMIEN CR (zolpidem tartate extended-release tablets) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION
2.1 Dosage in Adults
Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken once per night immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next-day impairment of driving and other activities that require alertness and/or psychomotor skills including the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e., subjective alertness). While pharmacodynamic tolerance or adaptation to some hypnotics may develop, it is not the same as physical dependency and can be interrupted by use of lower doses. Ambien CR should be taken as a single dose and should not be re-administered during the same night. The recommended initial doses for women and men are different because zolpidem clearance is lower in women [see Clinical Pharmacology (12.3)].

Treatment with AMIEN CR should be as short as possible. Extended treatment should not take place without re-evaluation of the patient’s status, since the risk of abuse and dependence increases with duration of treatment [see Drug Abuse and Dependence (9.3)].

2.2 Special Populations
Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Observed reactions include anaphylaxis and angioedema (see Warnings and Precautions (5.5)]. Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg once daily immediately before bedtime in these patients is 6.25 mg once daily immediately before bedtime. Avoid AMIEN CR use in patients with severe hepatic impairment as it may contribute to the emergence of new thinking or behavior abnormalities which 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.

Cases of angioedema involving the face, lips, glottis or larynx have also been reported in patients taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dysphagia, throat closing or nausea and vomiting that suggested anaphylaxis. Some patients had required medical therapy in the emergency department. If angioedema involves the larynx, immediate obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.5 Abnormal Thinking and Behavioral Changes
Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics, including AMIEN CR. While AMIEN CR is associated with decreased inhibition (e.g., aggressiveness and extraversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported. In controlled trials, <1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of patients treated with ambien 12.5 mg showed daytime sedation following bedtime reported hallucinations versus 0% treated with placebo [see Use in Specific Populations (8.4)]. There have been postmarketing reports of delirium with zolpidem use [see Adverse Reactions (6.2)]. It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above was drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.6 Use in Patients with Depression
In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be dispensed for the patient at one time.

5.7 Respiratory Depression
Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arterial Oxygen Index, together with a reduction in lower oxygen saturation and trend to lower times of oxygen desaturation below 90% and 95%, was observed in patients with mild to moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if AMIEN CR is prescribed to patients with compromised respiratory function or concomitant use with opioids or other CNS depressants. Observed reactions include anaphylaxis and angioedema (see Warnings and Precautions (5.5)]. Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg once daily immediately before bedtime in these patients is 6.25 mg once daily immediately before bedtime. Avoid AMIEN CR use in patients with severe hepatic impairment as it may contribute to the emergence of new thinking or behavior abnormalities which 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.

5.8 Precipitation of Hepatic Encephalopathy
Drugs affecting GABA receptors, such as zolpidem tartrate, 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 AMIEN CR 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)].

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

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

• Complex Sleep Behaviors

• CNS-Depressant Effects and Next-Day Impairment

• Contraindications

• Drug Interactions

6.1 Clinical Trials Experience
Associated with Discontinuation of Treatment
In 3-week clinical trials in adults and elderly patients (>65 years), 3.5% (7/201) patients receiving AMIEN CR 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.9% (22/16) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with AMIEN CR was a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e., subjective alertness). While pharmacodynamic tolerance or adaptation to some hypnotics may develop, it is not the same as physical dependency and can be interrupted by use of lower doses. AMIEN CR should be taken as a single dose and should not be re-administered during the same night. The recommended initial doses for women and men are different because zolpidem clearance is lower in women [see Clinical Pharmacology (12.3)].

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) [see Clinical Studies (14.2)].

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/double vision, reduced alertness, and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7–8 hours) is recommended.

Because AMIEN CR can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

5.2 CNS-Depressant Effects and Next-Day Impairment

5.3 Need to Evaluate for Comorbid Diagnoses

5.4 Hypnotics Have the Capacity to Depress Respiratory Drive

5.5 Abnormal Thinking and Behavioral Changes

5.6 Use in Patients with Depression

5.7 Respiratory Depression
zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=87) was discontinued after an attempted suicide.

Most Commonly Observed Adverse Reactions in Controlled Trials
During treatment with AMBIEN CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of AMBIEN CR were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating AMBIEN CR 12.5 mg, the adverse reaction profile was consistent with that reported in short-term trials, except for a higher incidence of anxiety (6.3% for AMBIEN CR versus 2.6% for placebo).

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 AMBIEN CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary 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 tables were derived from results of two placebo-controlled efficacy trials involving AMBIEN CR. These trials involved patients with primary insomnia who were treated for 3 weeks with AMBIEN CR at doses of 12.5 mg (Table 1) or 6.25 mg (Table 2), respectively. The tables include only AMBIEN CR. These trials involved patients with primary insomnia who were treated for 3 weeks with AMBIEN CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary 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 tables were derived from results of two placebo-controlled efficacy trials involving AMBIEN CR. These trials involved patients with primary insomnia who were treated for 3 weeks with AMBIEN CR at doses of 12.5 mg (Table 1) or 6.25 mg (Table 2), respectively. The tables include only adverse reactions occurring at an incidence of at least 1% for AMBIEN CR patients and with an incidence greater than that seen in the placebo patients.

### Table 1: Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Adults (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>AMBIEN CR 12.5 mg (N=102)</th>
<th>Placebo (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infecctions and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite disorder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations†</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Binge eating</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depersonalization</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mood swings</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stress symptoms</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Memory disorders‡</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Eye redness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2: Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Elderly (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>AMBIEN CR 6.25 mg (N=99)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reactions reported by at least 1% of patients treated with AMBIEN CR and at greater frequency than in the placebo group.
†Hallucinations included hallucinations NOS as well as visual and hypnagogic hallucinations.
‡Memory disorders include: memory impairment, amnesia, anterograde amnesia.
Adverse Events Observed during the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate, which are listed below.

Other Adverse Reactions Observed during the Premarketing Evaluation of AMBIEN CR

- Headache
- Dizziness
- Somnolence
- Burning sensation
- Dizziness postural
- Memory disorders
- Muscle contractions involuntary
- Paresthesia
- Tremor

Skin and subcutaneous tissue disorders
- Rash
- Urticaria

Musculoskeletal and connective tissue disorders
- Anarthria
- Muscle cramp
- Neck pain

Renal and urinary disorders
- Dysuria

Reproductive system and breast disorders
- Vulvovaginal dryness

General disorders and administration site conditions
- Influenza like illness
- Pyrexia

Dose Relationship for Adverse Reactions

Dose Relationship for Adverse Reactions

Other Adverse Reactions Observed during the Premarketing Evaluation of AMBIEN CR

Other treatment-emergent adverse reactions associated with participation in AMBIEN CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed during the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate

- Headache
- Dizziness
- Somnolence
- Burning sensation
- Dizziness postural
- Memory disorders
- Muscle contractions involuntary
- Paresthesia
- Tremor

Skin and subcutaneous tissue disorders
- Rash
- Urticaria

Musculoskeletal and connective tissue disorders
- Anarthria
- Muscle cramp
- Neck pain

Renal and urinary disorders
- Dysuria

Reproductive system and breast disorders
- Vulvovaginal dryness

General disorders and administration site conditions
- Influenza like illness
- Pyrexia

Injury, poisoning and procedural complications
- Neck injury

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.

Dose Relationship for Adverse Reactions

The frequencies presented, therefore, represent the proportion of the 3,669 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.

Central and peripheral nervous system: Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, insomnia, lethargy, light-headedness, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypnogogia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime sleep), speech disorder, stupor, tremor.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastrectasis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Other Adverse Reactions Observed during the Premarketing Evaluation of AMBIEN CR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Cardiovascular system: Frequent: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles. Rare: myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Other Adverse Reactions Observed during the Premarketing Evaluation of AMBIEN CR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Liver and biliary system: Frequent: acute hepatocellular, cholestatic or mixed liver injury with or without jaundice.

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

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

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

Drug Interactions

7. DRUG INTERACTIONS

7.1 CNS-Active Drugs

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem so that, 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.

Central and peripheral nervous system: Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, insomnia, lethargy, light-headedness, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypnogogia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime sleep), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuragia, neuritis, neuropathy, neuritis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastrectasis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

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

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

Lipid and lymphatic system: Frequent: abnormal hepatic function, increased SGPT, Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional: Frequent: hyperglycemia, thirst. Rare: glucose, hypercholesterolemia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periodontal edema.

Musculoskeletal system: Frequent: arthritis. Rare: arthritis, muscle weakness, sciatica, tendinitis.

Reproductive system: Frequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system: Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. 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, vision abnormal. Infrequent: eye irritation, eye pain, scintillate, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

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

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AMBIEN CR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Liver and biliary system: acute hepato cellular, cholestatic or mixed liver injury with or without jaundice (i.e., bilirubin >2 x ULN, alkaline phosphatase >2 x ULN, transaminase >5 x ULN).

Psychiatric disorders: delirium

7. DRUG INTERACTIONS

7.1 CNS-Active Drugs

CNS Depressants

Concomitant 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, 5.2)]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

Alcohol

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see Warnings and Precautions (5.1, 5.2)].

Opioids

The concomitant use of AMBIEN CR with opioids may increase the risk of respiratory depression. Limit dosage and duration of concomitant use of AMBIEN and opioids [see Dosage and Administration (2.3), Warnings and Precautions (5.7)].

Imipramine, Chlordiazepoxide

Imipramine 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)].

Sertraline

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

Fluxetine

After multiple doses of zolpidem tartrate and fluxetine 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)].
2 mg base/kg/day, which are approximately 2, 8, and 30 times the MRHD of 12.5 mg/day (10 mg zolpidem).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Neonates born to mothers using zolpidem late in the third trimester of pregnancy have been reported to experience symptoms of respiratory depression and sedation [see Clinical Considerations and Date].

Published data on the use of zolpidem during pregnancy have not reported a clear association with zolpidem and major birth defects. Oral administration of zolpidem to pregnant rats did not indicate a risk for adverse effects on fetal development at clinically relevant doses [see Date].

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

Clinical Considerations

Fetal/neonatal adverse reactions

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

Data

Human data

Published data from observational studies, birth registries, and case reports on the use of zolpidem during pregnancy do not report a clear association with zolpidem and major birth defects. There are limited postmarketing reports of severe to moderate cases of respiratory depression that occurred after birth in neonates whose mothers had taken zolpidem during pregnancy. These cases required artificial ventilation or intracranial suction. The majority of neonates recovered within hours to a few weeks after birth once treated.

Zolpidem has been shown to cross the placenta.

Animal data

Oral administration of zolpidem to pregnant rats during the period of organogenesis at 4, 20, and 100 mg base/kg/day, which are approximately 4, 20, and 100 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area, caused delayed fetal development (incomplete fetal skeletal ossification) at maternally toxic (ataxia) doses 20 and 100 times the MRHD based on mg/m² body surface area. Oral administration of zolpidem to pregnant rabbits during the period of organogenesis at 1, 4, and 16 mg base/kg/day, which are approximately 2, 8, and 30 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area caused embryo-fetal death and delayed fetal development (incomplete fetal skeletal ossification) at a maternally toxic (decreased body weight gain) dose 30 times the MRHD based on mg/m² body surface area.

Oral administration of zolpidem to pregnant rats from day 15 of gestation through lactation at 4, 20, and 100 mg base/kg/day, which are approximately 4, 20, and 100 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on a mg/m² body surface area, delayed offspring growth and decreased survival at doses 20 and 100 times, respectively, the MRHD based on mg/m² body surface area.

8.2 Lactation

Risk Summary

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

Clinical Considerations

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

8.4 Pediatric Use

AMBIEN CR 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 and nervous system disorders comprised the most frequent (≥5%) treatment emergent adverse reactions observed with zolpidem vomiting (placebo 0%, 15%, 5%, 5% with zolpidem 0.25, 3, 10, and 30 mg/kg), headache (20%, 8%, 3%, 3% and 15% with zolpidem), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [see Warnings and Precautions (5.5)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

FDA has not required pediatric studies of AMBIEN CR in the pediatric population based on these efficacy and safety findings.

8.5 Geriatric Use

A total of 99 elderly (>65 years of age) received daily doses of 6.25 mg AMBIEN CR in a 3-week placebo-controlled study. The adverse reaction profile of AMBIEN CR 6.25 mg in this population was similar to that of AMBIEN CR 12.5 mg in younger adults (≤64 years of age). Dizziness was reported in 8% of AMBIEN CR–treated patients compared with 3% of those treated with placebo.

The dose of AMBIEN CR in elderly patients is 6.25 mg/minimize the risk of adverse effects associated with impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see Warnings and Precautions (5.2)].

8.6 Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men. Cmax and AUC parameters of zolpidem from AMBIEN CR were, respectively, approximately 50% and 75% higher at the same dose in adult female subjects compared to adult male subjects. Between 6 and 12 hours after dosing, zolpidem concentrations were 2 to 3 fold higher in adult female compared to adult 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 CR for adult women is 6.25 mg, and the recommended dose for adult men is 6.25 or 12.5 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of AMBIEN CR in geriatric patients is 6.25 mg regardless of gender.

8.7 Hepatic Impairment

The recommended dose of AMBIEN CR in patients with mild to moderate hepatic impairment is 6.25 mg once daily immediately before bedtime. Avoid AMBIEN CR use in patients with severe hepatic impairment as it may contribute to encephalopathy [see Dosage and Administration (2.2), Warnings and Precautions (5.6), 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 Potential for 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 or one 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 drug 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 effects were 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

Use of AMBIEN CR may lead to development of physical and/or psychological dependence. This risk of dependence increases with dose and duration of treatment. The risk of abuse and dependence is also greater in patients with history of alcohol or drug abuse. AMBIEN CR should be used with extreme caution in patients with current or past alcohol or drug abuse.

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 be severe and includeConvulsion, sweating, vomiting, sweating, tremors, delirium.

The following adverse events, which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal, were reported during AMBIEN CR 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 asthenia. These adverse events occurred at an incidence of ≤1% or less. However, available data cannot provide a complete estimate of the incidence, if any, of dependence during treatment at recommended doses. There have been postmarketing reports of abuse, dependence and withdrawal with zolpidem.

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, cardiovas-

cular and/or respiratory compromise, and fatal outcomes have been reported.

10.2 Recommended Treatment

Carbohydrate and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdose, even if excretion occurs. The value of dialysis in the treatment of overdose of zolpidem has not been determined, although in vitro studies in animals have shown that the drug is not dialyzable.

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.
Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.89.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Zolpidem is a GABA A receptor positive modulator presumed to exert its therapeutic effects in the short-term treatment of insomnia through binding to the benzodiazepine site of GABA A receptors, increasing the frequency of chloride channel opening resulting in the inhibition of neuronal excitation.

12.2 Pharmacodynamics
Zolpidem binds to GABA A receptors with greater affinity for δ1 subunit relative to δ2 and δ3 subunit containing receptors. Zolpidem has no appreciable binding affinity for GABA B receptors. This binding profile may explain the relative absence of myorelaxant effects in animal studies.

Zolpidem has no appreciable binding affinity for dopaminergic D2, serotonergic 5HT2A, adrenergic, histaminergic or muscarinic receptors.

12.3 Pharmacokinetics
AMBIEN CR exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond three hours after administration. A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of AMBIEN CR 12.5 mg and of an immediate-release formulation of zolpidem tartrate (10 mg).

The terminal elimination half-life observed with AMBIEN CR (125 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg). The mean plasma concentration-time profiles are shown in Figure 1.

Figure 1: Mean Plasma Concentration-Time Profiles for AMBIEN CR (12.5 mg) and Immediate-Release Zolpidem Tartrate (10 mg)

In adult and elderly patients treated with AMBIEN CR, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

Absorption
Following administration of AMBIEN CR, administered as a single 12.5 mg dose in healthy male adult subjects, the mean peak concentration (C max) of zolpidem was 134 ng/mL (range: 88.9 to 197 ng/mL) occurring at a median time (T max) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy subjects compared the pharmacokinetics of AMBIEN CR 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C max were decreased by 23% and 30%, respectively, while median T max was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, AMBIEN CR should not be administered with or immediately after a meal.

Elimination
When AMBIEN CR was administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

Special Populations
Elderly
In 24 elderly (≥65 years) healthy subjects administered a single 6.25 mg dose of AMBIEN CR, the mean peak concentration (C max) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (T max) of 2.0 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.8 hours (range: 1.59 to 5.92 hours).

Hepatic impairment
AMBIEN CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency was compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean C max and AUC were found to be two times (250 vs 499 ng/mL) and five times (786 vs 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T max did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr) (see Dosage and Administration, 2.2, Warnings and Precautions 5.8, Use in Special Populations 8.7).

Renal impairment
AMBIEN CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl × V = 6.5 ± 1.5 L/min) undergoing hemodialysis three times a week, who were dose with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C max and half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics was not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

Drug Interactions

CNS depressants
Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression (see Warnings and Precautions 5.2). Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlophazamine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

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

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated (see Warnings and Precautions 5.2).

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C max was significantly higher (43%) and T max was significantly decreased (-53%). 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 showed no pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, no change in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and lortazepam 3 mg at steady-state levels in female volunteers resulted in a 34% increase in AUC C max 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%), C max (+36%) and T max of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem (see Drug Interactions 7.2).

Similarly, St. John’s wort, a CYP3A4 inducer, may also decrease the blood levels of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketocazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C max of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30%) along with an increase in the pharmacodynamic effects of zolpidem (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 cimetine/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 dogicin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg/kg/day. In mice, these doses are approximately 2, 9, and 40 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m 2 body surface area and in rats, these doses are approximately 4, 18, and 80 times the MRHD based on mg/kg body surface area. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (ipsoma, liposarcoma) were seen at the mid and high doses.

Mutagenesis
Zolpidem was negative in vitro (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and in vivo (mouse micronucleus) genetic toxicity assays.

Impairment of Fertility
Zolpidem was administered to rats at 4, 20, and 100 mg/kg/day, which are approximately 4, 20, and 100 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m 2 body surface area, prior to and during mating, and continuing in females through postpartum day 25. Zolpidem caused irregular estrus cycles and prolonged preimplantation intervals at the highest dose tested, which is
approximately 100 times the MRHD based on mg/m² body surface area. The NOAEL for these effects is 20 times the MRHD based on mg/m² body surface area. There was no impairment of fertility at any dose tested.

14 CLINICAL STUDIES
14.1 Controlled Clinical Trials
AMBIEN CR was evaluated in three placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM (V)™).

Adult outpatients (18–64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing AMBIEN CR 12.5 mg and placebo. AMBIEN CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. AMBIEN CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [PS]) during the first 2 nights of treatment and after 2 weeks of treatment. AMBIEN CR 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, patients treated with AMBIEN CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

In a 24-week double-blind, placebo controlled, randomized study in adult outpatients (18–64 years) with primary insomnia (N=1025), AMBIEN CR 12.5 mg administered as needed (3 to 7 nights per week) was superior to placebo over 24 weeks, on patient global impression regarding aid to sleep, and on patient reported specific sleep parameters for sleep induction and sleep maintenance with no significant increased frequency of drug intake observed over time.

14.2 Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs
Next-Day Residual Effects
In five clinical studies (three controlled studies in adults [18–64 years of age] administrated AMBIEN CR 12.5 mg and two controlled studies in the elderly [≥65 years of age] administrated AMBIEN CR 6.25 mg or 12.5 mg), the effect of AMBIEN CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with AMBIEN CR 12.5 mg and 6.25 mg using self-ratings of sedation.

During the 3-week studies, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg AMBIEN CR versus 2% of the placebo group; next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg AMBIEN CR versus 5% of the placebo group [see Adverse Reactions (6)]. In a 6-month study, the overall incidence of next-day somnolence was 5.7% in the AMBIEN CR group as compared to 2% in the placebo group.

Rebound Effects
Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two 3-week placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of AMBIEN CR. On the second night, there was no worsening compared to baseline in the AMBIEN CR group.

In a 6-month placebo-controlled study in which AMBIEN CR was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first 2 nights of treatment and after 2 weeks on treatment. AMBIEN CR 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, patients treated with AMBIEN CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

Next-Day Impairment
Tell patients that AMBIEN CR can cause next-day impairment even when used as prescribed, and that this risk is increased if dosing instructions are not carefully followed. Caution patients against driving and other activities requiring complete mental alertness the day after use. Inform patients that impairment can be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients [see Warnings and Precautions (5.2)].

Severe Anaphylactic and Anaphylactoid Reactions
Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur [see Warnings and Precautions (5.4)].

Sedation
Inform patients that use of AMBIEN CR late in the third trimester may cause respiratory depression and sedation in neonates. Advise mothers who used AMBIEN CR during the late third trimester of pregnancy to monitor neonates for signs of sleepiness (more than usual), breathing difficulties, or limpness [see Use In Specific Populations (8.1)].

16 HOW SUPPLIED/STORAGE AND HANDLING
AMBIEN CR 6.25 mg extended-release tablets are composed of two layers¹ and are coated, pink, round, biconvex, debossed with A– on one side and supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
<th>Bottle of 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0024-5501-31</td>
<td>bottle of 100</td>
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</table>

AMBIEN CR 12.5 mg extended-release tablets are composed of two layers¹ and are coated, blue, round, biconvex, debossed with A– on one side and supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
<th>Bottle of 100</th>
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<tr>
<td>0024-5521-31</td>
<td>bottle of 100</td>
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</table>

¹Layers are covered by the coating and are indistinguishable.

Manufactured by:
sandl-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY


Immediately if any of them occur

17 PATIENT COUNSELING INFORMATION
Advise patients to read the FDA-approved patient labeling (Medication Guide).

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

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

**AMBIEN CR® (ämˈbē-ən see ahr)**
(zolpidem tartrate)
extended-release tablets, for oral use, C-IV

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

**AMBIEN CR** may cause serious side effects, including:

- **Complex sleep behaviors.** After taking AMBIEN CR, 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. These activities may happen with AMBIEN CR whether or not you drink alcohol or take other medicines that make you sleepy. Some of these complex sleep behaviors have caused serious injury and death. People taking AMBIEN CR have reported:
  - sleep-walking
  - sleep-driving
  - making and eating food
  - talking on the phone
  - having sex

Stop taking AMBIEN CR and tell your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN CR.

### Do not take AMBIEN CR if you:

- have had complex sleep behaviors that happened after taking AMBIEN CR in the past. See “What is the most important information I should know about AMBIEN CR?”
- are allergic to zolpidem or any of the ingredients in AMBIEN CR. See the end of this Medication Guide for a complete list of ingredients in AMBIEN CR.

### Before taking AMBIEN CR, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts or actions
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- have sleep apnea
- have myasthenia gravis
- are pregnant or plan to become pregnant. Taking AMBIEN CR in the third trimester of pregnancy may harm your unborn baby:
  - Tell your healthcare provider if you become pregnant or plan to become pregnant during treatment with AMBIEN CR.
  - Babies born to mothers who take AMBIEN CR during the third trimester of pregnancy may have symptoms of breathing problems and sedation (such as sleepiness or low muscle tone).
- are breastfeeding or plan to breastfeed. AMBIEN CR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN CR.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. AMBIEN CR and other medicines can interact with each other causing serious side effects. AMBIEN CR may affect the way other medicines work, and other medicines may affect how AMBIEN CR works.

Especially tell your healthcare provider if you:

- take benzodiazepines
- take opioids as it may increase the risk of breathing problems (respiratory depression).
- take tricyclic antidepressants
- take other medicines that can make you sleepy or affect your breathing (including other zolpidem medicines)
- drink alcohol

You can ask your pharmacist for a list of medicines that interact with AMBIEN CR.

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

### How should I take AMBIEN CR?

- **Take AMBIEN CR exactly as prescribed.** Do not change your dose on your own. Tell your healthcare provider if you think AMBIEN CR is not working for you.
- **AMBIEN CR is for short-term use only.** Treatment with AMBIEN CR should be as short as possible because the risk of dependence increases the longer you are being treated.
- Take 1 AMBIEN CR tablet a night right before bedtime.
- **Do not take AMBIEN CR if you are not able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- You should not take AMBIEN CR with or right after a meal. AMBIEN CR may help you fall asleep faster if you take it on an empty stomach.
- **Do not take AMBIEN CR if you drank alcohol that evening or before bed.**
- Swallow AMBIEN CR tablets whole. Do not divide, crush, or chew AMBIEN CR tablets. If you cannot swallow AMBIEN CR tablets whole, tell your healthcare provider. You may need a different medicine.
- Call your healthcare provider if your sleep problems get worse or do not get better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much AMBIEN CR, call your healthcare provider or go to the nearest hospital emergency room right away.
What are the possible side effects of AMBIEN CR?

AMBIEN CR may cause serious side effects including:

- See “What is the most important information I should know about AMBIEN CR?”
- AMBIEN CR can make you sleepy or dizzy and can slow your thinking and motor skills. Next-day sleepiness is common, but can be serious. Because AMBIEN CR can make you sleepy or dizzy you are at a higher risk for falls.
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how AMBIEN CR affects you.
  - Do not drink alcohol or take opioids or other medicines that may make you sleepy or dizzy while taking AMBIEN CR without first talking to your healthcare provider. When taken with alcohol or other medicines that cause sleepiness or dizziness, AMBIEN CR may make your sleepiness or dizziness much worse.
- Severe allergic reactions. Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN CR.
- Abnormal thoughts and behavior. Symptoms include more outgoing or aggressive behavior than normal, confusion (delirium), acting strangely, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- Risk of suicide and worsening of depression. Worsening of depression, including suicidal thoughts and actions can happen during treatment with medicines like AMBIEN CR. Call your healthcare provider right away if you develop any thoughts of suicide, dying, or worsening depression during treatment with AMBIEN CR.
- Breathing problems. See “Before taking AMBIEN CR, tell your healthcare provider about all of your medical conditions, including if you:” Call your healthcare provider or get emergency medical help right away if you develop breathing problems during treatment with AMBIEN CR.
- Problems with your nervous system caused by severe liver disease (hepatic encephalopathy).
- Withdrawal symptoms. You may have withdrawal symptoms if you stop taking AMBIEN CR suddenly. Withdrawal symptoms can be serious and include stomach and muscle cramps, vomiting, sweating, shakiness, seizures, and confusion (delirium). Talk to your healthcare provider about slowly stopping AMBIEN CR to avoid withdrawal symptoms.

The most common side effects of AMBIEN CR include headache and dizziness. These are not all the side effects of AMBIEN CR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMBIEN CR?

- Store AMBIEN CR between at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep AMBIEN CR and all medicines out of reach of children.

General Information about the safe and effective use of AMBIEN CR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMBIEN CR for a condition for which it was not prescribed. Do not give AMBIEN CR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about AMBIEN CR that is written for healthcare professionals.

What are the ingredients in AMBIEN CR?

Active Ingredient: zolpidem tartrate

Inactive Ingredients:
The 6.25 mg tablets contain: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide.
The 12.5 mg tablets contain: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

Manufactured by:
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Bridgewater, NJ 08807
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For more information, go to www.ambiencr.com or call 1-800-633-1610.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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Rx Only