WARNINGS AND PRECAUTIONS

These highlights do not include all the information needed to use AMBIEN CR safely and effectively. See full prescribing information for AMBIEN CR. AMBIEN CR® (zolpidem tartrate extended-release) tablets, for oral use, C-IV Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.1) 02/2019

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

• Use the lowest dose effective for the patient and must not exceed a total of 12.5 mg daily (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)

Dosage Forms and Strengths

Extended-Release Tablets: 6.25 mg and 12.5 mg. Tablets not scored. (3)

CONTRAINDICATIONS

Known hypersensitivity to zolpidem (4)

WARNINGS AND PRECAUTIONS

• CNS-depressant effects: Impaired alertness and motor coordination, including risk of morning impairment. Caution patients against driving and other activities requiring complete mental alertness the morning after use. (5.1)
• Need to evaluate for comorbid diagnoses: Re-evaluate if insomnia persists after 7 to 10 days of use. (5.2)
• Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)
• "Sleep-driving" and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)
• Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.5)
• Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.6)
• Hepatic Impairment: Avoid AMBIEN CR use in patients with severe hepatic impairment. (5.7)
• Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.8, 5.9)

ADVERSE REACTIONS

Most commonly observed adverse reactions (>10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (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 www.fda.gov/medwatch.

DRUG INTERACTIONS

• CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.1, 7.1)
• Imipramine: Decreased alertness observed (7.1)
• Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
• CYP3A4 inducers (rifampin or St. John’s wort): Combination use may decrease effect (7.2)
• Ketoconazole: Combination use may increase effect (7.2)

USE IN SPECIFIC POPULATIONS

• Pregnancy: May cause respiratory depression and sedation in neonates with exposure late in the third trimester. (8.1)
• Lactation: A lactating woman may pump and discard breast milk during treatment and for 23 hours after AMBIEN 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. (5.4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide Revised: 02/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Dosage in Adults
  2.2 Special Populations
  2.3 Use with CNS Depressants
  2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 CNS-Depressant Effects and Next-Day Impairment
  5.2 Need to Evaluate for Comorbid Diagnoses
  5.3 Severe Anaphylactic and Anaphylactoid Reactions
  5.4 Abnormal Thinking and Behavioral Changes
  5.5 Use in Patients with Depression
  5.6 Respiratory Depression
  5.7 Precipitation of Hepatic Encephalopathy
  5.8 Withdrawal Effects
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
7 DRUG INTERACTIONS
  7.1 CNS-Active Drugs
  7.2 Drugs that Affect Drug Metabolism via Cytochrome P450
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Lactation
  8.3 Pediatric Use
  8.4 Geriatric Use
  8.5 Drug Interactions
  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
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMBIEN CR (zolpidem tartrate extended-release tablets) is indicated for the 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) in duration [see Clinical Studies (14)].

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 only 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 at follow-up visits. Patients who may require lower doses may include older patients, the higher morning blood levels of either 6.25 or 12.5 mg 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 CR should not exceed 12.5 mg once daily immediately before bedtime. AMBIEN CR should be taken as a single dose and should not be divided, crushed, or chewed. 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 CR in these patients is 6.25 mg once daily 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 recommended dose of AMBIEN CR in these patients is 6.25 mg once daily 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)].

3 USE WITH CNS DEPRESSANTS

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

4 ADMINISTRATION

AMBIEN CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of AMBIEN CR may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

AMBIEN CR is an extended-release tablet containing 6.25 or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

AMBIEN CR 6.25 mg tablets are pink, round, bi-convex, and debossed with A~ on one side. AMBIEN CR 12.5 mg tablets are blue, round, bi-convex, and debossed with A~ on one side.

4 CONTRAINDICATIONS

AMBIEN CR 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 CR is a central nervous system (CNS) depressant and can impair daytime function in some patients treated with sedative-hypnotics, including AMBIEN CR. Some of these changes included decreased inhibition (i.e., aggressiveness and extraversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

5.2 Risk for Sleep-Related Driving and Other Activity Impairment

In order to minimize this risk a full night of sleep (7–8 hours) is recommended.

5.3 Other Complex Behaviors

Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.4 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavioral changes have been reported in patients treated with sedative/hypnotics, including AMBIEN CR. Some of these changes included 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 pediatric patients treated with Ambien CR 6.25 mg taken at time 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 sedative-hypnotic-naive as well as in sedative-hypnotic experienced patients. Although "sleep-driving" has been observed in patients taking AMBIEN CR alone at therapeutic doses, the coadministration of alcohol and other CNS depressants increases the risk of such behaviors, as does the use of AMBIEN CR at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of AMBIEN CR should be strongly considered if a patient reports 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 usually do not remember these events. Amnesia, anxiety and other neuro- psychological changes have also been reported.

Coadministration of AMBIEN CR with other sedative-hypnotics increases the risk of such behaviors. It is not clear whether a particular instance of the abnormal behaviors listed above is due to 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 consideration of the need for discontinuation of AMBIEN CR and the introduction of other treatment and careful and immediate evaluation of the patient.

5.5 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 prescribed for the patient at any one time.

5.6 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressive effects at hypnotic doses in healthy subjects or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Acuval 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 respiratory impairment when treated with zolpidem compared to placebo. Since sedative- hypnotics have the capacity to depress respiratory drive, precautions should be taken if AMBIEN CR is prescribed to patients with compromised respiratory function. Postmarketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been received. Treatment with other sedative- hypnotics, including AMBIEN CR should be used with caution in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.7 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 AMBIEN 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)].

5.8 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:

• CNS-depressant effects and next-day impairment

• Abnormal thinking and behavior changes, and complex behaviors [see Warnings and Precautions (5.4)]

Abnormal thinking and behavior changes, and complex behaviors [see Warnings and Precautions (5.4)]

• Withdrawal effects [see Warnings and Precautions (5.8)]

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 AMBIEN CR 6.25 mg were discontinued due to adverse reactions as compared to 0.4% (8/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with AMBIEN CR was somnolence (1%).

In a 6-month study in adult patients (18–64 years of age), 8.5% (57/669) of patients receiving AMBIEN CR 12.5 mg were discontinued due to adverse reactions as compared to 4.6% on placebo (16/349) discontinued treatment due to an adverse reaction. Reactions most commonly associated with discontinuation of AMBIEN CR included anxiety (anxiety, restlessness or agitation) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo.

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients (n=51) were treated with zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=35) were associated with impaired concentration, continuing or aggravated depression, anxiolytic reaction; one patient treated with placebo (n=37) 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, the most frequently observed treatment-emergent 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 (8.3% for AMBIEN CR versus 2% 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 uniform terminology. The frequency and incidence of adverse reactions were summarized separately for each group of drug trials and are provided under a different set of conditions. However, the cited frequencies cannot be compared with figures obtained from other clinical trials involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited frequencies cannot be compared with figures obtained from other clinical trials involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited frequencies cannot be compared with figures obtained from other clinical trials involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions.
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>Infections 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>
<tr>
<td>Altered visual depth perception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Athetaesthesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td></td>
<td></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>Otis externa</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Apathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness postural</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Memory disorders§</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Muscle contractions involuntary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Central and peripheral nervous system: Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, agitation, delirium, lightheadedness, vertigo, impaired attention, abnormal coordination, impaired cognitive performance, foundering, difficulty concentrating, dysthymia, emotional lability, hallucinations, hypotension, illusion, leg cramps, migraine, nervousness, paresthesia, insomnia, sleep-related impairment, disrupted sleep, nightmares, panic attacks, paraesthesia, psychological impairment, suicide attempt, suicidal ideation. Rare: aggressive reaction, apathy, anxiety, increased appetite, decreased libido, delusion, dementia, depersonalization, dysphoria, feeling strange, hallucinations, hypotension, hysteria, intoxicated feeling, mania, reactions, neuritis, neuroupathy, panic attacks, changes in mood, paraesthesia, personality disorder, somnambulism, suicide attempt, tetany, yawning.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, abdominal distension, flatulence, gastroenteritis. Rare: enteritis, nephrolithiasis, vomiting, enteritis, nephrolithiasis.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphopenia, neutropenia, macrocytic anemia, purpura, thrombosis.

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

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

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: glucose, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, portal edema.

Musculoskeletal system: Infrequent: arthritis. Rare: arthrosis, muscle weakness, scoliosis, tendinitis.

Reproductive system: Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasms, 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, sciatica, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, labial abnormal, papilloma, photosis.


6.2 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 hepatoxiccellular, cholestatic or mixed liver injury with or without jaundice (i.e., bilirubin >2 x ULN, alkaline phosphatase ≥2 x ULN, transaminase ≥2 x ULN). 7. DRUG INTERACTIONS

7.1 CNS-Active Drugs

Coadministration 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 for safety and efficacy in healthy volunteers in single-dose interaction studies for several CNS drugs.

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

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

7.2 Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to induce or inhibit CYP3A4 may affect exposure to zolpidem. The effect of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known. CYP3A4 Inducers

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of 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, 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

Risk Summary

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction*</th>
<th>AMBIEN CR 6.25 mg (N=99)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck injury</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>2 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysturia</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvar vaginal dryness</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 0</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.

†Memory disorders include: memory impairment, amnesia, anterograde amnesia.
impairment as it may contribute to encephalopathy.

8.7 Hepatic Impairment

AMBIEN CR in geriatric patients is 6.25 mg regardless of gender. The recommended dose of zolpidem from AMBIEN CR were, respectively, approximately 50% and 75% higher at the same dose in men and women. The recommended dose of AMBIEN CR is 6.25 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)).

9.5 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.

9.6 Gender Difference in Pharmacokinetics

Women clear zolpidem 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 clearance levels of zolpidem 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.

9.7 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. In situations where it may be necessary, use should be guided by the patient's hepatic function (see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Pharmacology (12.3)).

9.9 Drug Abuse and Dependence

9.9.1 Controlled Substance

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

9.9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects. Addiction is a chronic, primary, 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 use despite knowing the harmful effects. 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.

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions.

The following adverse events, which are considered to meet the 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 adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Postmarketing 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, cardiovas-
cular and/or respiratory compromise, and fatal outcomes have been reported.

10.2 Recommended Treatment

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

As with the management of all overdosage, 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 overdosage.

11 DESCRIPTION

AMBIEN CR contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A receptor positive modulator of the inhibitory glycine receptor. AMBIEN CR (zolpidem tartrate) extended-release tablets is available in 6.25 mg and 12.5 mg strength tablets for oral administration. Zolpidem tartrate is N,N,N-trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 784.98.

AMBIEN CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The 6.25 mg AMBIEN CR tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, and titanium dioxide. The 12.5 mg AMBIEN CR tablet contains the following inactive ingredients: 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.

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 is a GABA A receptor with greater affinity for GABA 1 subunit relative to GABA 2 and GABA 3 subunit containing receptors. Zolpidem has no appreciable binding affinity for GABA 5 subunit containing GABA A 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 (12.5 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 (Cmax) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/mL) occurring at a median time (Tmax) 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 with administration while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and Cmax were decreased by 23% and 30%, respectively, while median Tmax 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. Distribution
Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Metabolism
Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion. Elimation
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: 1.82 to 4.05 hrs). Special Populations

Elderly
In 24 elderly (≥65 years) healthy subjects administered a single 6.25 mg dose of AMBIEN CR, the mean peak concentration (Cmax) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (Tmax) 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 2.9 hours (range: 1.59 to 5.50 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 Cmax and AUC were found to be twice (250 vs 499 ng/mL) and five times (788 vs 4,203 ng·hr/mL), respectively, in hepatically compromised patients. Tmax did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr) ([see Dosage and Administration (2.2), Warnings and Precautions (5.7), Use in Specific 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 Clcr = 6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for Cmax, Tmax, half-life, and AUC between the first and last day of drug administration when baseline adjustment adjustments were made. Zolpidem was not hemodialyzable. Noaccumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics was not significantly altered in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. Drug Interactions
CNS-depressants
Coadministration of zolpidem with other CNS depressants increases the risk of CNS depression ([see Warnings and Precautions (5.1)], Zolpidem may be administered in combination with other CNS-depressants. IMIPRAMINE up to 200 mg/day significantly increased the mean plasma concentration of zolpidem by approximately 50%. During a 14-day parallel-group study in healthy subjects, zolpidem Cmax was significantly higher (43%) and Tmax was significantly decreased (-53%). Pharmacokinetics of sevroleine and N-desmethylsevroleine were unaffected by zolpidem. A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels revealed no statistically significant effect on any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was evidence of an additive effect in psychomotor performance. Drugs that affect drug metabolism via cytochrome P450
Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors other than P450 enzymes on the pharmacokinetics of zolpidem is unknown. A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in AUCmax of zolpidem tartrate. 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 (-79%), Cmax (-93%), and Tmax (-36 %) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem ([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 ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30%) along with an increase in the pharmacodynamic effects of zolpidem ([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 simetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

14 CLINICAL STUDIES
14.1 Controlled Clinical Trials
A single-dose 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 IV). 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 [LPS] 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.

Elderly outpatients (≥65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing AMBIEN CR 6.25 mg and placebo. AMBIEN CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. AMBIEN CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks of treatment. AMBIEN CR 6.25 mg improved sleep latency 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, in 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 the clinical trials (three controlled studies in adults [18-64 years of age] administered AMBIEN CR 12.5 mg and two controlled studies in the elderly [≥65 years of age] administered 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 single nighttime dose. In addition, no evidence of next-day residual effects was detected with AMBIEN CR 12.5 mg or 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 0% 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 night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

15 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:

- NDC Number: 0024-5501-31
  - Size: bottle of 100

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:

- NDC Number: 0024-5521-31
  - Size: bottle of 100

1Layers are covered by the coating and are indistinguishable.


17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients and their families about the benefits and risks of treatment with AMBIEN 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. Inform patients or caregivers that AMBIEN CR should be taken only as prescribed.

CNS-Depressant Effects and 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.

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

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

Tolerance, Abuse, and Dependence

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

Administration Instructions

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

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with AMBIEN CR. Advise 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)].

Lactation

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

MEDICATION GUIDE

AMBIEN CR® (əmˈbe-ən see ahr) (zolpidem tartrate) extended-release tablets C-IV

Read the Medication Guide that comes with AMBIEN CR 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 CR?

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

AMBIEN CR may cause serious side effects that you may not know are happening to you. These side effects include:

- sleepiness during the day
- not thinking clearly
- act strangely, confused, or upset
- “sleep-walking” or doing other activities when you are asleep like:
  - eating
  - talking
  - having sex
  - driving a car

Call your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN CR. You should not drive a car or do things that require clear thinking the day after you take AMBIEN CR.

Do not take AMBIEN CR if you:

- drank alcohol that evening or before bed.
- take other medicines that can make you sleepy. Taking AMBIEN CR with other drugs can cause side effects. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take AMBIEN CR with your other medicines.
- cannot get a full night’s sleep.

What is AMBIEN CR?

AMBIEN CR is a sedative-hypnotic (sleep) medicine. AMBIEN CR is used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep
- waking up often during the night

AMBIEN CR is not recommended for use in children under the age of 18 years.

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

Who should not take AMBIEN CR?

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

AMBIEN CR may not be right for you. Before starting AMBIEN CR, tell your healthcare provider about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. Talk to your healthcare provider about the risk to your unborn baby if you take AMBIEN CR.
- Using AMBIEN CR in the last trimester of pregnancy may cause breathing difficulties or excess sleepiness in your newborn. Monitor for signs of sleepiness (more than usual), trouble breathing, or limpness in the newborn if AMBIEN CR is taken late in pregnancy.
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 nonprescription medicines, vitamins and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects. Do not take AMBIEN CR 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 CR?
- See “What is the most important information I should know about AMBIEN CR?”
- Take AMBIEN CR exactly as prescribed. Only take 1 AMBIEN CR tablet a night if needed.
- Do not take AMBIEN CR if you drank alcohol that evening or before bed.
- 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.
- Take AMBIEN CR Tablets whole. Do not break, crush, dissolve or chew AMBIEN CR tablets before swallowing. If you cannot swallow AMBIEN CR tablets whole, tell your healthcare provider. You may need a different medicine.
- 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 problems.
- If you take too much AMBIEN CR or overdose, get emergency treatment.

What are the possible side effects of AMBIEN CR?
AMBIEN CR may cause serious side effects including:
- getting out of bed while not being fully awake and doing an activity that you do not know you are doing. (See “What is the most important information I should know about AMBIEN CR?”)
- 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, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN CR.

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 CR.

The most common side effects of AMBIEN CR are:
- headache
- sleepiness
- dizziness
- drowsiness the next day after you take AMBIEN CR

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 CR. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMBIEN CR?
Store AMBIEN CR at room temperature, 59°F to 77°F (15°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 share AMBIEN CR with other people, even if they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about AMBIEN CR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMBIEN CR that is written for healthcare professionals.

For more information, go to www.ambiencr.com or call 1-800-633-1610.

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.

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

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Revised: February 2019
©2019 sanofi-aventis U.S. LLC

ACR-FPLR-SL-FEB19 Rx Only