WARNINGS AND PRECAUTIONS

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

INDICATIONS AND USAGE

AMBEN 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)

WARNING: COMPLEX SLEEP BEHAVIORS

See full prescribing information for complete boxed warning.

Complex sleep behaviors including 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)

CONTRAINDICATIONS

• 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

• 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. (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: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.4)
• Abnormal Thinking and Behavioral Changes: Changes including decreased inhibition, bizarre behavior, agitation, and depersonalization have been reported. Immediately evaluate any new onset behavioral changes. (5.5)
• Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.6)
• Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.7)
• Hepatic Impairment: Avoid AMBIEN CR use in patients with severe hepatic impairment. (5.8)
• Withdrawal Effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.9, 5.3)

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 (5.2, 6.1)
• 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. (5.5, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2020
Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions involving 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 AMBIEN CR can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falling.

5.3 Need to Evaluate for Comorbid Diagnoses
Because sleep disturbances may be the presenting manifestation of a physical or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. Use of AMBIEN CR for 7 to 10 days of treatment may be viewed as the minimum period of time needed to judge response to therapy and the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e., sleep latency, sleep efficiency, and subjective assessment of alertness).

5.4 Severe Anaphylactic and Anaphylactoid Reactions
Cases of anaphylaxis involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional features of anaphylactic shock such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. 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.

5.5 Abnormal Thinking and Behavioral Changes
Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics, including AMBIEN CR. Some of these changes included decreased inhibition (e.g., aggressiveness and overexuberance that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

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 overdose 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.

5.7 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 Annual 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 severe obstructive sleep apnea 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 reported. The risk of respiratory depression should be considered prior to prescribing AMBIEN CR in patients with respiratory impairment including sleep apnea and myelusin gravis.

5.8 Precipitation of Hepatic Encephalopathy
When treating GABA A receptor, benzodiazepine, or zolpidem, hepatic encephalopathy has 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 normal subjects. Avoid AMBIEN CR use in patients with severe hepatic impairment as it may contribute to encephalopathy (see 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 [see Warnings and Precautions (5.1)]
• CNS-Depressant Effects and Next-Day Impairment [see Warnings and Precautions (5.2)]
• Severe Anaphylactic and Anaphylactoid Reactions [see Warnings and Precautions (5.4)]
• Abnormal Thinking and Behavioral Changes [see Warnings and Precautions (5.5)]
• Withdrawal Effects [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience
Associated with Discontinuation of Treatment
In 3-week clinical trials in adult and elderly patients (>65 years), 3.5% (7/201) patients receiving AMBIEN CR 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.3% (6/201) patients receiving placebo. The 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% (57/675) of patients receiving AMBIEN CR 12.5 mg as compared to 4.6% on placebo (10/224) discontinued treatment due to an adverse reaction as compared to 0.3% (3/104) of patients on placebo. The most commonly associated with discontinuation of AMBIEN CR included dizziness, dry mouth, somnolence, and fatigue.

The use of AMBIEN CR with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if AMBIEN CR is taken with less than a full night of sleep remaining (7 to 8 hours). If longer than the recommended dose is taken, if coadministered with other CNS depressants, with alcohol or coadministered with other drugs that increase the blood levels of zolpidem. Patients should be warned against driving and other activities requiring complete mental alertness if AMBIEN CR is taken in these circumstances (see Dosage and Administration (2), Clinical Studies (14.2)).
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 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</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>1</td>
</tr>
<tr>
<td>Asthenopia</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>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>AMBIEN CR 6.25 mg (N=99)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<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>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin wrinkling</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Neck pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Body temperature increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Social circumstances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to poisonous plant</td>
<td>1</td>
<td>0</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.

### 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</th>
<th>AMBIEN CR 12.5 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>1</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td>1</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>
</tbody>
</table>
### 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 Adverse Reaction</th>
<th>AMBIEN CR 6.25 mg (N=99)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders</strong></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>1</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry throat</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal dryness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck injury</td>
<td>1</td>
<td>0</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, amnestic amnesia.

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.

Other Adverse Reactions Observed During the Premarketing Evaluation of AMBIEN CR

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.

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.

7 DRUG INTERACTIONS

7.1 CNS-Active Drugs

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. 

### Table 3: Drug-Drug Interaction Studies

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Additive</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Additive</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Additive</td>
<td></td>
</tr>
</tbody>
</table>

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

CYP3A4 Inhibitors

Ketoconazole

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage 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 intratracheal intubation. The majority of neonates recovered within hours to a few weeks after birth once treated.

Zolpidem has been shown to cross the placenta.

Animal data

Oral administration of zolpidem to pregnant rats during the period of organogenesis at 4, 20, and 100 mg base/kg/day, which are approximately 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 32 times the MRHD of 12.5 mg (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.

Oral administration of zolpidem to rat pups from day 1 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 breastfeeding 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 and manage accordingly.

Monitor neonates exposed to AMBIEN CR during pregnancy and labor for signs of excess sedation, hypotonia, and respiratory depression and manage accordingly.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

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

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, 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

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 muscular 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 of 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, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

10.2 Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Inotropic 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 supportive measures. Sedating drugs must be withheld following zolpidem overdose, even if agitation occurs. The value of dialysis in the treatment of overdose 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 overdose.

11 DESCRIPTION

AMBIEN CR contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) receptor positive modulator of the imidazopyridine class. AMBIEN CR (zolpidem tartrate) extended-release tablets is available in 6.25 mg and 12.5 mg strengths for oral administration.

Chemically, zolpidem is N,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 378.94.
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 binds to GABA A receptors with greater affinity for δ3 subunit relative to δ2 and δ3 subunit containing receptors. Zolpidem has no appreciable binding affinity for δ5 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 5HT1, 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)**

[Insert figure showing 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 when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean Cmax, Tmax and area under the curve (AUC) were increased 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. In healthy adult volunteers, the mean elimination half-life was 2.0 hours (range: 1.23 to 3.74 hr).

**Elimination**
In elderly outpatients (N=231), use in specific populations (8.7), use in elderly patients (8.7), use in children (8.7), use in renal failure (8.8), use in hepatic failure (8.9), and use in pregnancy (8.10).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**
Zolpidem was administered to rats and mice for 2 years at oral doses of 4, 18, and 80 mg base/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/m² body surface area and in rats, these doses are approximately 4, 18, and 80 times the MRHD based on mg/m² body surface area. No evidence of carcinogenic potential was observed in these studies. In mice, rats, and hamsters (loma, lispariom) were seen at the mid and high doses. Mutagenesis
Zolpidem was found to be 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 base/kg/day, which are approximately 4, 20, and 100 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area, prior to and during mating, and continuing in females through postpartum day 25. Zolpidem caused irregular estrus cycles and prolonged preantral 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-IV). Adult outpatients (N=231) 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 (polygraph), subjective measures, and sleep duration (by increasing latency to persistent sleep). Elderly outpatients (N=231) 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 subjective measures (polygraph), sleep duration (by increasing latency to persistent sleep), and sleepiness (by decreasing LPS).
Precautions (5.2)

round, biconvex, debossed with A~ on one side and supplied as:

T olerance, Abuse, and Dependence

not be taken with or immediately after a meal. Advise patients NOT to take AMBIEN CR if they drank alcohol that evening.

T olerance, Abuse, and Dependence

AMBIEN CR 6.25 mg extended-release tablets are composed of two layers decreased consciousness may increase the risk of falls in some patients immediately if any of them occur 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] 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 was 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 night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

AMBIEN CR 6.25 mg extended-release tablets are composed of two layers 1 and are coated, pink, round, biconvex, debossed with A- on one side and supplied as:

NDC Number Size
0024-5501-31 bottle of 100

AMBIEN CR 12.5 mg extended-release tablets are composed of two layers 1 and are coated, blue, round, biconvex, debossed with A- on one side and supplied as:

NDC Number Size
0024-5521-31 bottle of 100

1 Layers 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. 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)].

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 [see Warnings and Precautions (5.2)].

Severe Anaphylactic and Anaphylactoid Reactions

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

Suicide

Tell patients to immediately report any suicidal thoughts. Alcohol and other Drugs

Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients never 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 (7–8 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 breast milk 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® (əmˈbē-ən 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 including complex sleep behaviors that have caused serious injury and death. 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 (complex sleep behaviors). The next morning, you may not remember that you did anything during the night. These activities may occur with AMBIEN CR whether or not you drink alcohol or take other medicines that make you sleepy. Reported activities include:

• driving a car (“sleep-driving”)
• making and eating food
• talking on the phone
• having sex
• sleep-walking

Stop taking AMBIEN CR and 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:

• have ever experienced a complex sleep behavior (such as driving a car, making and eating food, talking on the phone, or having sex while not being fully awake) after taking AMBIEN CR.
• 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.
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:
- drowsiness the next day after you take AMBIEN CR

AMBIEN CR may help you fall asleep faster if you take it on an empty stomach.

- abnormal thoughts and behavior. Symptoms include more outgoing or aggressive behavior than normal, confusion, acting strangely, 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: August 2019

©2019 sanofi-aventis U.S. LLC

ACR-FPLR-SL-SEP20 Rx Only