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Ambien CR
(zolpidem tartrate) Extended-Release Tablets

Ambien CR

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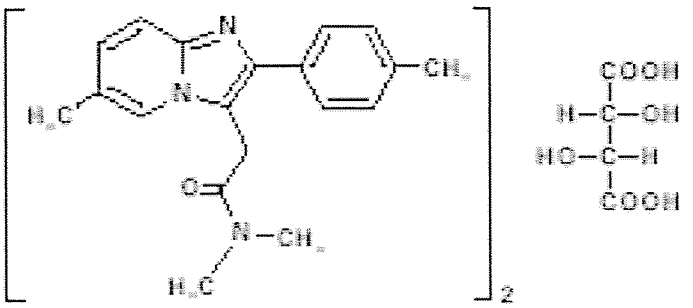
DRUG DESCRIPTION

Ambien CR contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Ambien CR (zolpidem tartrate extended-release tablets) is available in 6.25 mg and 12.5 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-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 764.88. Ambien CR (zolpidem tartrate) 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 (zolpidem tartrate) tablet contains the following inactive ingredients: 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 Ambien CR (zolpidem tartrate) 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.

What are the possible side effects of zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)?

Report any new or worsening symptoms to your doctor, such as: depression, anxiety, aggression, agitation, confusion, unusual thoughts, hallucinations, memory problems, changes in personality,

risk-taking behavior, decreased inhibitions, no fear of danger, or thoughts of suicide or hurting yourself.

Stop using zolpidem and call your doctor at once if you have a serious side effects:

- chest pain, fast or irregular heartbeat, feeling short of breath;
- trouble breathing or swallowing; or
- feeling like you might pass...

Read All Potential Side Effects and See Pictures of Ambien CR »

What are the precautions when taking zolpidem tartrate (Ambien CR)?

Before taking zolpidem, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: kidney disease, liver disease, mental/mood problems (such as depression, thoughts of suicide), personal or family history of regular use/abuse of drugs/alcohol/other substances, personal or family history of sleepwalking, lung/breathing problems (such as chronic obstructive pulmonary disease-COPD, sleep apnea), a certain muscle disease (myasthenia gravis).

Do not drive, use machinery, or do any activities that require...

Read All Potential Precautions of Ambien CR »

Last reviewed on RxList: 5/10/2010

Medical Editor: Charles Patrick Davis, MD, PhD

This monograph has been modified to include the generic and brand name in many instances.

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INDICATIONS

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].

DOSAGE AND ADMINISTRATION

The dose of Ambien CR (zolpidem tartrate) should be individualized.

Dosage in adults

The recommended dose of Ambien CR (zolpidem tartrate) for adults is 12.5 mg once daily immediately before bedtime. The total Ambien CR (zolpidem tartrate) dose should not exceed 12.5 mg per day.

Special populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. The recommended dose of Ambien CR (zolpidem tartrate) in both of these patient populations is 6.25 mg once daily immediately before bedtime [see **WARNINGS AND PRECAUTIONS**].

Use with CNS depressants

Dosage adjustments may be necessary when Ambien CR (zolpidem tartrate) is combined with other CNS depressant drugs because of the potentially additive effects [see**WARNINGS AND PRECAUTIONS**].

Administration

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

HOW SUPPLIED

Dosage Forms And Strengths

Ambien CR (zolpidem tartrate) is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

Ambien CR (zolpidem tartrate) 6.25 mg tablets are pink, round, bi-convex, and debossed with A~ on one side. Ambien CR (zolpidem tartrate) 12.5 mg tablets are blue, round, bi-convex, and debossed with A~ on one side.

Ambien CR (zolpidem tartrate) 6.25 mg tablets are composed of two layers* and are coated, pink, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5501-31	bottle of 100
0024-5501-50	bottle of 500
0024-5501-10	carton of 30 unit dose
0024-5501-34	carton of 100 unit dose

Ambien CR (zolpidem tartrate) 12.5 mg tablets are composed of two layers* and are coated, blue, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5521-31	bottle of 100
0024-5521-50	bottle of 500
0024-5521-10	carton of 30 unit dose
0024-5521-34	carton of 100 unit dose

Store between 15°-25° C (59°-77°F). Limited excursions permissible up to 30° C (86°F)

*Layers are covered by the coating and are indistinguishable.

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SIDE EFFECTS

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

- Serious anaphylactic and anaphylactoid reactions [see**WARNINGS AND PRECAUTIONS**)
- Abnormal thinking, behavior changes, and complex behaviors [see**WARNINGS AND PRECAUTIONS**]
- Withdrawal effects [see**WARNINGS AND PRECAUTIONS**]
- CNS-depressant effects [see**WARNINGS AND PRECAUTIONS**]

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 (zolpidem tartrate) 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.9% (2/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with Ambien CR (zolpidem tartrate) 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 (zolpidem tartrate) 12.5 mg 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 (zolpidem tartrate) 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, and depression (depression, major depression or depressed mood) 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 were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

Most commonly observed adverse reactions in controlled trials: During treatment with Ambien CR (zolpidem tartrate) in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of Ambien CR (zolpidem tartrate) were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating Ambien CR (zolpidem tartrate) 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 (zolpidem tartrate) versus 2.6% for placebo).

Adverse reactions observed at an incidence of ≥ 1% in controlled trials: The following tables enumerate treatment-emergent adverse reaction frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien CR (zolpidem tartrate) 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 (zolpidem tartrate) . These trials involved patients with primary insomnia who were treated for 3 weeks with Ambien CR (zolpidem tartrate) 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 (zolpidem tartrate) 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)

Body System/Adverse Reaction*	Ambien CR (zolpidem tartrate) 12.5 mg (N = 102)	Placebo (N = 110)
Infections and infestations		
Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
Metabolism and nutrition disorders		
Appetite disorder	1	0
Psychiatric disorders		
Hallucinations**	4	0
Disorientation	3	2
Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0
Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
Nervous system disorders		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders***	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
Eye disorders		
Visual disturbance	3	0

Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
Ear and labyrinth disorders		
Vertigo	2	0
Tinnitus	1	0
Respiratory, thoracic and mediastinal disorders		
Throat irritation	1	0
Gastrointestinal disorders		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux disease	1	0
Vomiting	1	0
Skin and subcutaneoustissuedisorders		
Rash	1	0
Skin wrinkling	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0
Reproductive system and breast disorders		
Menorrhagia	1	0
General disorders and administration site conditions		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
Investigations		
Blood pressure increased	1	0
Body temperature increased	1	0
Injury, poisoning and procedural complications		
Contusion	1	0
Social circumstances		
Exposure to poisonous plant	1	0

*Reactions reported by at least 1% of patients treated with Ambien CR (zolpidem tartrate) and at greater frequency than in the placebo group.
**Hallucinations included hallucinations NOS as well as visual and hypnogogic 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)

Body System/Adverse Reaction*	Ambien CR (zolpidem tartrate) 6.25 mg (N=99)	Placebo (N=106)
Infections and infestations		

Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
Nervous system disorders		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders**	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		
Flatulence	1	0
Vomiting	1	0
Skin and subcutaneoustissuedisorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system andbreastdisorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

*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.

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 (zolpidem tartrate) : Other treatment-emergent adverse reactions associated with participation in

Ambien CR (zolpidem tartrate) studies (those reported at frequencies of < 1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed During the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate: Immediate-release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Ambien, they were not necessarily caused by it.

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

Autonomic nervous system: Frequent: dry mouth. Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole: Frequent: asthenia. Infrequent: chest pain, edema, falling, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

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

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

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

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

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

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

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

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

Respiratory system: Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, 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, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

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

Read the Ambien CR (zolpidem tartrate) Side Effects Center for a complete guide to possible side effects

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DRUG INTERACTIONS

CNS-active drugs

Since the systematic evaluations of zolpidem in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

An immediate-release formulation of zolpidem tartrate was evaluated in healthy subjects in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated [see**WARNINGS AND PRECAUTIONS**].

A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following five consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem Cmax was significantly higher (43%) and Tmax was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

Drugs that affect drug metabolism via cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes has not been carefully evaluated.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female subjects between five consecutive daily doses of rifampin (600 mg) and a single dose of an immediate-release formulation of zolpidem tartrate (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), Cmax (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

A randomized double-blind crossover interaction study in twelve healthy subjects showed that co-administration of a single 5 mg dose of immediate-release zolpidem tartrate with ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem by a factor of 1.3 and increased the total AUC of zolpidem by a factor of 1.7 compared to zolpidem alone and prolonged the elimination half-life by approximately 30% along with an increase in the pharmacodynamic effects of zolpidem. Caution should be used when ketoconazole is given with zolpidem and consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together. Patients should be advised that use of Ambien CR (zolpidem tartrate) with ketoconazole may enhance the sedative effects.

Other drugs with no interaction with zolpidem

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in normal subjects.

Drug-laboratory test interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

Drug Abuse And Dependence

Controlled substance

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

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, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg effects were difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

Dependence

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

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events, 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. Post-marketing reports of abuse, dependence and withdrawal have been received.

Read the Ambien CR Drug Interactions Center for a complete guide to possible interactions

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WARNINGS

Included as part of the **PRECAUTIONS** section.

PRECAUTIONS

Need to evaluate for co-morbid diagnoses

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

Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema 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 symptoms 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.

Abnormal thinking and behavioral changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g. aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation and depersonalization. In controlled trials, < 1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations [see **Use in Specific Populations**].

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 with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naive as well as in sedative-

hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with Ambien CR (zolpidem tartrate) alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien CR (zolpidem tartrate) appears to increase the risk of such behaviors, as does the use of Ambien CR (zolpidem tartrate) at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien CR (zolpidem tartrate) should be strongly considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably.

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions including completed suicides), have been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Withdrawal effects

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs [see **Drug Abuse and Dependence**].

CNS depressant effects

Ambien CR (zolpidem tartrate) , like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien CR (zolpidem tartrate) should only be taken immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien CR (zolpidem tartrate) . Ambien CR (zolpidem tartrate) showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien CR (zolpidem tartrate) is administered with such agents because of the potentially additive effects.

Special populations

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien CR (zolpidem tartrate) dosage is 6.25 mg in such patients to decrease the possibility of side effects [see DOSAGE AND ADMINISTRATION]. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien CR (zolpidem tartrate) in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien CR (zolpidem tartrate) in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with an immediate-release formulation of zolpidem tartrate (10 mg) when compared to placebo. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be taken if Ambien CR (zolpidem tartrate) is

prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Ambien CR (zolpidem tartrate) should be used with caution in patients with sleep apnea syndrome or myasthenia gravis.

Data in end-stage renal failure patients repeatedly treated with an immediate-release formulation of zolpidem tartrate (10 mg) did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored [see CLINICAL PHARMACOLOGY].

A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with Ambien CR (zolpidem tartrate) 6.25 mg in patients with hepatic compromise, and they should be closely monitored [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Use in patients with depression: As with other sedative/hypnotic drugs, Ambien CR (zolpidem tartrate) should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Use in pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD given an immediate-release oral solution of zolpidem tartrate, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [see **Use in Specific Populations**].

Patient Counseling Information

Prescribes or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics, should counsel them in its appropriate use, and should instruct them to read the accompanying Medication Guide [see **Medication Guide**].

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

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when Ambien CR (zolpidem tartrate) is taken with alcohol or other central nervous system depressants [see **WARNINGS AND PRECAUTIONS**]. 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.

In addition, patients should be advised to report all concomitant medications to the prescriber. Patients should be instructed to report events such as "sleep-driving" and other complex behaviors immediately to the prescriber.

Administration instructions

Patients should be counseled to take Ambien right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Ambien CR (zolpidem tartrate) tablets should not be crushed, divided, or chewed, and should not be taken with or immediately after a meal. Advise patients NOT to take Ambien CR (zolpidem tartrate) when drinking alcohol.

Nonclinical Toxicology

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. In mice, these doses are approximately 2, 9, and 40 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) on mg/m^2 basis. In rats, these doses are approximately 4, 18, and 80 times the MRHD on a mg/m^2 basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

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

Impairment of fertility: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg or approximately 4, 20, and 100 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. The no-effect dose for these findings is approximately 20 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

Use In Specific Populations

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Ambien CR (zolpidem tartrate) in pregnant women. Ambien CR (zolpidem tartrate) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the Ambien CR (zolpidem tartrate) maximum recommended human dose (MRHD) of 12.5 mg/day (approximately 10 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg (approximately 4, 20 and 100 times the MRHD on a mg/m^2 basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m^2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg (approximately 2, 8 and 30 times the MRHD on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 8 times the MRHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg (approximately 4, 20 and 100 times the MRHD on a mg/m^2 basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m^2 basis.

Neonatal complications

Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS depressants.

Children born to mothers taking sedative-hypnotic drugs may be at some risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy.

Labor and delivery

Ambien CR (zolpidem tartrate) has no established use in labor and delivery [see **Pregnancy**].

Nursing mothers

Zolpidem is excreted in human milk. Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hr). The effect of zolpidem on the nursing infant is not known. Caution should be exercised when Ambien CR (zolpidem tartrate) is administered to a nursing woman.

Pediatric use

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) [see **WARNINGS AND PRECAUTIONS**]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

FDA has not required pediatric studies of Ambien CR (zolpidem tartrate) in the pediatric population based on these efficacy and safety findings.

Geriatric use

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

The dose of Ambien CR (zolpidem tartrate) in elderly patients 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**].

Last reviewed on RxList: 5/10/2010
This monograph has been modified to include the generic and brand name in many instances.
