

ApoB Trumps Cholesterol as a CHD Predictor

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Plasma concentration of apolipoprotein B is a slightly better predictor of coronary heart disease than is non-HDL cholesterol and a much better predictor than is LDL cholesterol, reported Dr. Tobias Pischon of the Harvard School of Public Health, Boston, and his associates. This finding is sure to add to the controversy over which lipid measurement is

the best for assessing both coronary risk and treatment efficacy. According to current National Cholesterol Education Program guidelines, LDL cholesterol is recommended as the primary target for lipid-lowering therapy, HDL cholesterol is considered a secondary treatment target, and apolipoprotein B (apoB) is not considered a target at all, the investigators said. In the first large prospective study to directly compare these three measures, apoB was the best predictor of coronary heart

disease (CHD) risk (Circulation 2005;112:3375-83). The researchers used a database of more than 51,000 male health professionals who had been followed every 2 years since 1986 to identify 243 subjects who had developed CHD during a 6-year study period and 496 matched control subjects who had not developed the disease. The baseline level of apoB was the strongest predictor of CHD, with a relative risk of 2.98. The concentration of non-HDL cholesterol also was strongly

predictive, with a relative risk of 2.75, and the LDL cholesterol level was predictive but less so, with a relative risk of 2.07. “The practical application of our findings,” the investigators wrote, would be to switch from assessing LDL and non-HDL cholesterol in screening and treatment of CHD to assessing apoB instead. However, the cost of such a switch relative to the potential improvement in risk assessment “needs to be further evaluated,” they said. ■

Ambien CR™ (zolpidem tartrate extended-release tablets) BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset). (See Clinical Pharmacology: Controlled trials supporting safety and efficacy.)

The clinical trials performed in support of efficacy were both 3 weeks in duration, although the final formal assessments of sleep latency and maintenance were performed after 2 weeks of treatment.

CONTRAINDICATIONS

Ambien CR is contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation.

WARNINGS

Since 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 which 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. Because some of the important adverse effects of zolpidem appear to be dose related (see *Precautions and Dosage and Administration*), it is important to use the smallest possible effective dose, especially in the elderly.

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. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has 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.

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*).

Zolpidem, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien CR should only be ingested 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 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 is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

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 dosage is 6.25 mg in such patients (see *Dosage and Administration*) to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with zolpidem in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien CR 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 tartrate 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. However, precautions should be observed if Ambien CR is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency in patients receiving immediate-release zolpidem tartrate, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with immediate-release zolpidem tartrate 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. A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with Ambien CR 6.25 mg in patients with hepatic compromise, and they should be closely monitored.

Use in depression: Sedative/hypnotic drugs should be administered with caution to patients with signs or symptoms of depression. 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 least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for patients: Patient information is printed at the end of this insert. To assure safe and effective use of Ambien CR, this information and instructions provided in the patient information section should be discussed with patients.

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions

CNS-active drugs: An immediate-release formulation of zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem tartrate revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem tartrate 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 tartrate produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. 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 tartrate was demonstrated.

A single-dose interaction study with zolpidem tartrate 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 tartrate 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 tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylertraline were unaffected by zolpidem.

Since the systematic evaluations of Ambien CR in combination with other CNS-active drugs showed no clinically significant interaction, 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.

Drugs that affect drug metabolism via cytochrome P450: 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 an immediate-release formulation of zolpidem tartrate (10 mg) given five 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 volunteers 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%), C_{max} (~58%), and $T_{1/2}$ (~36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

Other drugs: A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on dipoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley rats for two years at dietary dosages of 4, 18, and 80 mg/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day (40 and 80 times the maximum recommended human dose [MRHD] of Ambien CR 12.5 mg [10 mg zolpidem base], respectively, on a mg/m² basis).

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* mammalian gene forward mutation assay in mouse lymphoma cells, and an *in vitro* unscheduled DNA synthesis in rat hepatocytes. Zolpidem was not clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes or in an *in vivo* micronucleus test in mice.

Impairment of Fertility: Zolpidem tartrate was administered by oral gavage to Sprague-Dawley rats at doses of 4, 20, or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on post partum Day 25. Zolpidem administered at 100 mg base/kg was associated with irregular estrus cycles and prolonged pre-coital intervals, but did not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day (20 times the MRHD of Ambien CR on a mg/m² basis).

Pregnancy

Teratogenic effects: Pregnancy Category C. Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg base/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal and embryo/fetal toxicity was 4 mg base/kg/day (4 times the MRHD of Ambien CR on a mg/m² basis). Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (up to 30 times the MRHD of Ambien CR, on a mg/m² basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternbrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was below 1 mg base/kg/day (0.2-times the MRHD of Ambien CR, on a mg/m² basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day (8 times the MRHD of Ambien CR on a mg/m² basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg and higher. Decreased maternal body weight gain as well as evidence on non-secreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg and higher and decreased pup survival at maternal doses of 100 mg base/kg. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg (4 times the MRHD of Ambien CR on a mg/m² basis).

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

Nonteratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and delivery: Ambien CR has no established use in labor and delivery. (See also *Pregnancy*.)

Nursing Mothers: Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6; 0.3 hr). Between 0.004% and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown. In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m².

The use of Ambien CR in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness of Ambien CR in patients below the age of 18 have not been established.

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

ADVERSE REACTIONS

Associated with discontinuation of treatment: In clinical trials with Ambien CR, 3.5% of 201 patients receiving 6.25-mg or 12.5-mg of Ambien CR discontinued treatment because of an adverse event. Events most commonly associated with discontinuation were somnolence (1.0%) and dizziness (1.0%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given immediate-release zolpidem tartrate 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.

Incidence in controlled clinical trials

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

Adverse events observed at an incidence of ≥1% in controlled trials of Ambien CR: The following enumerates treatment-emergent adverse events 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 investigations 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 was 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. Included are only adverse events occurring at an incidence of at least 1% for Ambien CR patients and with an incidence greater than that seen in the placebo patients.

Incidences of Treatment-Emergent Adverse Events in a 3-Week Placebo-Controlled Clinical Trial in Adults [events reported by at least 1% of patients treated with Ambien CR 12.5 mg (n=102) and at greater frequency than in the placebo group (n=110)]. Infections and infestations: Influenza (3% vs 0%); Gastroenteritis (1% vs 0%); Labyrinthitis (1% vs 0%). **Metabolism and nutrition disorders:** Appetite disorder (1% vs 0%). **Psychiatric disorders:** Hallucinations (including hallucinations NOS as well as visual and hypnagogic hallucinations) (4% vs 0%); Disorientation (3% vs 2%); Anxiety (2% vs 0%); Depression (2% vs 0%); Psychomotor retardation (2% vs 0%); Binge eating (1% vs 0%); Depersonalization (1% vs 0%); Disinhibition (1% vs 0%); Euphoric mood (1% vs 0%); Mood swings (1% vs 0%); Stress symptoms (1% vs 0%). **Nervous system disorders:** Headache (19% vs 16%); Somnolence (15% vs 2%); Dizziness (12% vs 5%); Memory disorders (including memory impairment, amnesia, anterograde amnesia) (3% vs 0%); Balance disorder (2% vs 0%); Disturbance in attention (2% vs 0%); Hypoesthesia (2% vs 1%); Ataxia (1% vs 0%); Paresthesia (1% vs 0%). **Eye disorders:** Visual disturbance (3% vs 0%); Eye redness (2% vs 0%); Vision blurred (2% vs 1%); Altered visual depth perception (1% vs 0%); Asthenopia (1% vs 0%). **Ear and labyrinth disorders:** Vertigo (2% vs 0%); Tinnitus (1% vs 0%). **Respiratory, thoracic and mediastinal disorders:** Throat irritation (1% vs 0%). **Gastrointestinal disorders:** Nausea (7% vs 4%); Constipation (2% vs 0%); Abdominal discomfort (1% vs 0%); Abdominal tenderness (1% vs 0%); Frequent bowel movements (1% vs 0%); Gastroesophageal reflux disease (1% vs 0%); Vomiting (1% vs 0%). **Skin and subcutaneous tissue disorders:** Rash (1% vs 0%); Skin wrinkling (1% vs 0%); Urticaria (1% vs 0%). **Musculoskeletal and connective tissue disorders:** Myalgia (4% vs 0%); Neck pain (1% vs 0%). **Reproductive system and breast disorders:** Menorrhagia (1% vs 0%). **General disorders and administration site conditions:** Fatigue (3% vs 2%); Asthenia (1% vs 0%); Chest discomfort (1% vs 0%). **Investigations:** Blood pressure increased (1% vs 0%); Body temperature increased (1% vs 0%). **Injury, poisoning and procedural complications:** Contusion (1% vs 0%). **Social circumstances:** Exposure to poisonous plant (1% vs 0%).

Incidences of Treatment-Emergent Adverse Events in a 3-Week Placebo-Controlled Clinical Trial in Elderly patients [events reported by at least 1% of patients treated with Ambien CR 6.25 mg (n=99) and at greater frequency than in the placebo group (n=106)]. Infections and infestations: Nasopharyngitis (6% vs 4%); Lower respiratory tract infection (1% vs 0%); Otitis externa (1% vs 0%); Upper respiratory tract infection (1% vs 0%). **Psychiatric disorders:** Anxiety (3% vs 2%); Psychomotor retardation (2% vs 0%); Apathy (1% vs 0%); Depressed mood (1% vs 0%). **Nervous system disorders:** Headache (14% vs 11%); Dizziness (8% vs 3%); Somnolence (6% vs 5%); Burning sensation (1% vs 0%); Dizziness postural (1% vs 0%); Memory disorders (including memory impairment, amnesia, anterograde amnesia) (1% vs 0%); Muscle contractions involuntary (1% vs 0%); Paresthesia (1% vs 0%); Tremor (1% vs 0%). **Cardiac disorders:** Palpitations (2% vs 0%). **Respiratory, thoracic and mediastinal disorders:** Dry throat (1% vs 0%). **Gastrointestinal disorders:** Flatulence (1% vs 0%); Vomiting (1% vs 0%). **Skin and subcutaneous tissue disorders:** Rash (1% vs 0%); Urticaria (1% vs 0%). **Musculoskeletal and connective tissue disorders:** Arthralgia (2% vs 0%); Muscle cramp (2% vs 1%); Neck pain (2% vs 0%). **Renal and urinary disorders:** Dysuria (1% vs 0%). **Reproductive system and breast disorders:** Vulvovaginal dryness (1% vs 0%). **General disorders and administration site conditions:** Fatigue (3% vs 2%); Asthenia (1% vs 0%). **Injury, poisoning and procedural complications:** Neck injury (1% vs 0%).

Dose relationship for adverse events: There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Other Adverse Events Observed During the Premarketing Evaluation of Ambien CR: Other treatment-emergent adverse events associated with participation in Ambien CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed During the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate: 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 immediate-release zolpidem. All reported treatment-emergent adverse events are included, except 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 immediate-release zolpidem, 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, tetanus.

Body as a whole: Frequent: allergy, asthenia, back pain, influenza-like symptoms. Infrequent: chest pain, edema, falling, fatigue, 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: Frequent: palpitation. Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrastokes, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system: Frequent: ataxia, confusion, depression, dizziness, drowsiness, drugged feeling, euphoria, headache, insomnia, lethargy, lightheadedness, vertigo. Infrequent: abnormal dreams, agitation, amnesia, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoaesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleep disorder, 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: abdominal pain, diarrhea, dyspepsia, hiccup, nausea. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting. 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, hypercholesterolemia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

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

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

Respiratory system: Frequent: pharyngitis, sinusitis, upper respiratory infection. Infrequent: bronchitis, coughing, dyspnea, rhinitis. Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages: Frequent: rash. 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.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Zolpidem tartrate is classified as a Schedule IV controlled substance under the Controlled Substances Act. Examples of other drugs placed in Schedule IV include benzodiazepines (diazepam, alprazolam, etc) and the non-benzodiazepine hypnotics (zaleplon and eszopiclone).

Abuse and dependence: Studies of abuse potential in former drug abusers found that the effects of single doses of an immediate-release formulation of zolpidem tartrate (Ambien) 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

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 U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in 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. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

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.

OVERDOSAGE

Signs and symptoms: In postmarketing reports of overdose with immediate-release zolpidem tartrate alone, impairment of consciousness has ranged from somnolence to light coma. There was one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose of the immediate-release product). Overdose cases involving multiple CNS-depressant agents, including zolpidem tartrate, have resulted in more severe symptomatology, including fatal outcomes.

Recommended treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem tartrate overdose, even if excitation 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.

Poison control center: As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

DOSAGE AND ADMINISTRATION

The dose of Ambien CR should be individualized.

Ambien CR is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Ambien CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of Ambien CR may be slowed by ingestion with or immediately after a meal.

The recommended dose of Ambien CR for adults is 12.5 mg immediately before bedtime. Elderly or debilitated patients may be especially sensitive to the effects of zolpidem. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. The recommended dose of Ambien CR in these patients is 6.25 mg immediately before bedtime (see *Precautions*).

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