Keep Patients on Acamprosate Through Relapse

BY TIMOTHY F. KIRN

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SCOTTSDALE, ARIZ. — Alcohol abusers who take acamprosate and relapse are still better off continuing to take the drug because they have an improved chance of achieving abstinence, company

Pooled data from three separate, controlled trials of the drug suggest that almost three times more patients treated through a relapse eventually achieve a period of abstinence, compared with controls, Dr. Eugene Schneider said in a poster presentation at the annual meeting of the American Academy of Addiction Psychiatry.

In the studies, most of the participants relapsed at some point. Of the 372 people treated with acamprosate (1,998 mg/day), 72% relapsed, and 85% of 375 placebocontrol patients relapsed. One of the trials lasted 13 weeks, one lasted 48 weeks, and the third lasted 52 weeks.

Overall, 13% of the acamprosate-treated individuals who relapsed were subsequently abstinent for the remainder of the study and an additional 20% who relapsed were abstinent at their final study evaluation. The comparable figures for the control patients were 5% and 10%, respectively, said Dr. Schneider, an associate director for medical affairs at Forest Laboratories Inc., New York.

Acamprosate-treated patients who achieved a period of abstinence after relapse had a greater mean number of days of abstinence than did controls: 24 days vs. 14 days. In the patients who relapsed but eventually became abstinent for the remainder of the study, the treated patients were more likely to have had a longer abstinence: a mean of 28 days for the treated patients, compared with 12 days for the control patients.

"It is worthwhile treating patients through a relapse," Dr. Schneider said in

Ambien CR™® BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien CR (zolpidem tartate extended-release tablets) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by valke 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 tartate 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 sychiatric 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 CMS depressants. Visual and auditory hallucinations have been reported to seedative/hypnotics.

interrations

active drugs: a inere are no specific laboratory tests recommended.
j interactions

active drugs: An immediate-release formulation of zolpidem tartrate was
lated in healthy volunteers in single-dose interaction studies for several
drugs. A study involving haloperidol and zolpidem tartrate revealed
fifect of haloperidol on the pharmacokinetics or pharmacodynamics of
dem. Imipramine in combination with zolpidem tartrate produced no pharpokinetic interaction other than a 20% decrease in peak levels of
ramine, but there was an additive effect of decreased alertness. Similarly,
promazine in combination with zolpidem tartrate produced no pharmacoic interaction, but there was an additive effect of decreased alertness and
homotor performance. The lack of a drug interaction following single-dose
inistration does not predict a lack following of pronic administration.

additive effect on psychomotor performance between alcohol and
dem tartrate was demonstrated.

Since the systematic evaluations of Ambien CR 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 zolljedm. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zoloidem.

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 flumazenii, however, no significant alterations in zolpidem pharmacokinetics.

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, manistering as dose-related lettargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related ternaty and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related ternaty of des 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 zolp-dem tartrate to pregnant Himalayan Albinor 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 stemebrae in viable fetuses. Feratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was below 1 mg base/kg/day (c 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 (g times the MRHD of Ambien CR on an gm/m² basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day (a times the MRHD of Ambien CR on an gm/m² basis).

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Adverse events observed at an incidence of ≥1% in controlled trials of Ambien CR: The following enumerates treatment-emergent adverse event 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.

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 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=170]). Intections and intestations: Intellneta (3% vs 0%). Secontenteritis (1% vs 0%), Labyrinthitis (1% vs 0%). Metabolism and untirium disorders: Appetted disorder (1% vs 0%). Secontenteritis (1% vs 0%), Psychomotor retardation (2% vs 0%). Secontenteritis (1% vs 0%), Psychomotor retardation (2% vs 0%). Secondarion (1% vs 0%), Psychomotor retardation (2% vs 0%). Secondarion (1% vs 0%), Psychomotor retardation (2% vs 0%). Secondarion (1% vs 0%). Distribution (1% vs 0%). Distribution (1% vs 0%). Distribution (1% vs 0%). Secondarion (1% vs 0%). Distribution (1% vs 0%). Secondarion (1% vs 0%). Sec

Iverse events.

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

dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, pareis, 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 settena, otitis media.

Liver and biliary system: Infrequent: abnormal hepatic functions.

Tipes Zuster, uttus externa, ottus media.

Liver and billary system: Infrequent: abnormal hepatic function, increased SGPT. Rare: billisubinemia, increased SGOT.

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

Injectionessereim, ryperingerm, instance and proposed and

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.

nary incontinence. Rare. acute renal failure, dysuria, micrutrition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

PRUG ABUSE AND DEPENDENCE

Controlled substance. Zolpidem tartrate is classified as a Schedule IV controlled substance and. 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) 4 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 dysphota and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomitting, 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 seadtive/hypnotic withdrawal were reported during U.S. clinical trials soflowing placebos 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 abuse hours 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 othe

management of hypnotic drug product overdosage.

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 or 2019/dem tartrate for oral administration. Ambien CR extended-elease tablets should be swallowed whole, and not be divided, crushed, or hewed. The effect of Ambien CR may be slowed by ingestion with or immeditely after a meal.

The recommended dose of Ambien CR for adults is 12.5 mg immediately sefore bedtime.

re bedtime. derly or debilitated patients may be especially sensitive to the effects of idem. Patients with hepatic insufficiency do not clear the drug as rapidly as nals. The recommended dose of Ambien CR in these patients is 6.25 mg rediately before bedtime (see Precautions).

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Ambien CR™ (zolpidem tartrate extended-release tablets)

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