Straight Talk Can Address Alcohol Abuse in Teens

More than 35% of adults who have an alcohol problem say they were binge drinkers before age 19.

BY DAMIAN MCNAMARA

MIAMI BEACH — Lorena M. Siqueira, M.D., has a straightforward way of dealing with teenaged binge drinkers: Ask them their alcohol consumption, present the facts, and don't give lectures.

Nearly 14 million adults, or 1 in 13, in the United States abuse alcohol or are alcohol dependent, according to the National Institute on Alcohol Abuse and Alcoholism. Intervening with teens may make a longterm difference since more than 35% of adults with an alcohol problem say they were binge drinkers before age 19.

A binge can be defined as a self-destructive and unrestrained drinking bout, lasting at least a couple of days, at least once in the preceding 2 weeks. Binge drinking also can be defined as five or more alcoholic drinks in a row for males, or four or more drinks for females on a single occasion.

We used to think the brain was fully formed by adolescence, but now we know it continues to develop into the early 20s.

may have long-lasting effects on intellectual capabilities," said Dr. Siqueira, director of the division of adolescent medicine at Miami Children's Hospital.

Address binge drinking as early as possible, Dr. Siqueira advised. "Some children are already alcohol dependent when you see them. Some start as young as 9 or 10 years old," she said at a pediatric update sponsored by the hospital.

Teenagers who binge drink are more likely to drive drunk, fight, carry a weapon, drop out of school, engage in risky sexual behavior, or use illicit drugs. Teenage binge drinking is "one of the strongest predictors of binge drinking through the college years."

One role of the physician is to identify alcohol abuse. Blackouts, depression, sleep

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disorders, chronic abdominal pain, liver dysfunction, sexual dysfunction, and sexually transmitted infections (STIs) are common signs. For example, 60% college women diagnosed with an STI were drunk

at the time of acquiring the infection, Dr. Siqueira said. Screen all children for use of alcohol, including beer, wine, and distilled spirits. Once a potential problem is identified, evaluate the extent of drinking. Ask questions about how many days they drink alcohol, how many drinks they have on those days, and whether there are times when they are unable to stop drinking once they start.

Almost every state allows minors to consent for care for drugs or alcohol without parental consent. If you do not have time or do not feel comfortable treating alcohol dependence, refer them, she suggested.

'The best way to get [children] to change, rather than lecturing to them, is to present them with as many facts as you can," Dr. Siqueira said. If a patient refuses to admit to having an issue with alcohol, ask the patient to define when it will become a problem. Some will say alcohol would be a problem if their grades dropped, for example.

"Appeal to their vanity," Dr. Siqueira said. "Tell them drinking gives them bad breath and makes them gain weight."

Recommended tools and resources for physicians include the CRAFFT (mnemonic) screen for alcohol use (Arch Pediatr. Adolesc. Med. 1999;153:591-6), the National Council on Alcoholism and Drug Dependence (www.ncadd.org), and the National Institute on Alcohol Abuse and Alcoholism (www.niaaa.nih.gov).

Resources for patients and parents include Alateen (www.alateen.org), the "Make a Difference: Talk to Your Child About Alcohol" pamphlet (www.niaaa. nih.gov/publications/makediff.htm), and the Join Together initiative (www.join together.org).



INDICATIONS AND USAGE
LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep
laboratory studies, LUNESTA administered at bedtime decreased sleep latency and
improved sleep maintepance.

CONTRAINDICATIONS

Because sleep disturbances may be the presenting mannestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia ehould 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. Worsaring of insomnia or the emergence of new thinking or behavior ahommallites maybe the consequence of an unrecognized psy-chiatric or physical disorder. Such findings have emerged during the course of treat-ment with sedative-hyponic drugs, including LUMESTA. Beasuse some of the impor-tant adverse effects of LUMESTA appear to be dose-related, it is important to use the lowest possible effective dose, sepecially in the elderly (see DOSAGE AND ADMINIS-TRATION in the Full Prescribing Information).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hymnotics. Some of these changes may be char association with the use of sedative/hymorics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes hav included bizarre behavior, agitation, hallucinations, and depersonalization. Amness and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hymorics.

It can rarely be determined with certainty whether a particular instance of the abnor in call nately be deed inmed with relating whether a particular instance on the author mail behaviors listed above are drug-induced, spontaneous in origin, or a result of ar underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation. Following rapid dose decrease or abrupt discontinuation of the use of sedative/hyptomis chiral to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE). withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE). LIMESTA, like other hyponicis, has CUS-depressant affects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty failing seleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alterness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA, LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, articonvolvants, antificial princes. anticonvolsarits, animisatimes, entaine, and outer trudys that mainteness produce. CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents because of the potentially additive effects.

Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, d impairment, hallucinations, impaired coordination, dizziness, and lightheadedness. 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 diderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see DOSAGE AND ADMINISTRATION in the Full Prescribing Information).

Use In Patients With Concomitant Illuses: Clinical experience with escopiolone in patients with concomitant illness is limited. Escopiolone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopicione. Caution is advised, 2.5-fold higher (7 mg) than the recommended dose of escopicione. Caution is advised however, if LUNESTA is prescribed to patients with compromised respiratory function however, if LUNESTA is prescribed to patients with compromised respiratory function. The dose of LUNESTA should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mid or moderate hepatic impairment, bed dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of escopicione is excreted unchanged in the urine. The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYPSA4, such as ketoconazole, while taking LUNESTA. Downward dose adjustment is also recommended when LUNESTA is administered with agents having known CNS-depressant effects.

Use In Patients With Depression: Sective/hypnotic drugs should be administered with caution to gatients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patiens, and protective measures may be required. Intentional overdose is more common in this group of patients, at optional 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 in the complete prescribing information

Laboratory Tests: There are no specific laboratory tests recommended

Chis-Active Drugs

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine
20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam
2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine: Coadministration of eszopidone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alter-ation in the pharmacokinetics of either drug.

Drugs That Inhibit CYP3A4 (Ketoconazde): CYP3A4 is a major metabolic pathway for elimination of eszopicione. The AUC of eszopicione was increased 2.2-fold by coadministration of ketoconazde. consistency of Verteconscole, a potent subtition of CYP3A4. 400, mg failly for 5 faths: C₁₀₀ and t₁₀, were increased 1.4 hold and 3.4 hold. respectively, other strong inhibits of CYP3A4 (e.g., traconazole, clarithronycin, nefazodone, troleandomycin, ritonavir, nefinavir) would be executed to behave similarly. Drugs That Induce CYP3A4 (Rilampicin): Racemic zopicione exposure was decreased 80% by concomitant use of infampicin, a potent inducer of CYP3A4. A similar effect would be expected with expositions.

similar effect would be expected with eszopicione. Drugs Highly Bound To Plasma Protelle: Eszopicione is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopicione is not expected to be sensitive to alterations in protein binding. Administration of eszopicione 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

Drugs With A Narrow Therapeutic Index

Digoxin: A single dose of eszopictione 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

and 0.25 mg daily for the next 5 days. Warfarin: Eszopicione 3 mg administered daily for 5 days did not affect the pharma-cokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacody-namic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impaiment of Fertility
Carcinogenesis In a carcinogenicity study in Sprague-Dawley rats in which eszopi
clone was given by oral gavage, no ircraeses in tumors were seen; plasma levels
(AUC) of eszopicione at the highest dose used in this study (16 mg/kg/day) are esti-

Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day, Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas in subcroun. The increase is thought to be due to preceded levels. is unknown. The increase in thyroid lumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHU. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral garage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—Lie., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

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Mutagenesis: Escopicione was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an in vivo mouse bone marrow micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese namster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* %2p-postlabeling DNA adduct assay, and in an in vivo mouse bone marrow chromosomal aberration and

micronucleus assay. Impairment Of Fertility: Eszopicione was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopicione decreased fertility, probably because of effects in both males and females. Wet freated with the fitigliest becoming pregnant when both males and females were treated with the fitigliest dose; the no-effect dose in both sexes was 5 mg/kg (16 tinses the MRHD on a mg/m² basis). Other effects included increases merimplantation loss (no-effect dose 25 mg/kg), ahoromal estrus cycles (no-effect dose 25 mg/kg), and odecreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy
Pregna

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

Labor And Delivery: LUNESTA has no established use in labor and delivery.

Nursing Mothers: It is not known whether LUNESTA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LUNESTA is administered to a nursing woman. Pediatric Use: Safety and effectiveness of eszopiclone in children below the age of 18

lader into been essabilished.

Geratric Uses: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopicione were 65 to 56 years of age. The overall pattern of adverse events for elderly subjects (median age – 71 years) in 2-west studies with nighttime dosing of 2 mg eszopicione was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the delerly population.

rketing development program for LUNESTA included eszopicloni rependancing overeignment of the program of the product of the program of the program of the provinced studies approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, wital signs, weights, laboratory analyses, and ECGs.

weights, laboratory analyses, and ECVs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

Adverse Findings Observed in Placebo-Controlled Trials

Adverse Events Resulting in Discontinuation of Treatment: In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received parallergroup united intals in the elevity, 3.5% or 200 patients with received 2 mg LUNESTA, and 1.4% of 7.2 patients who received 2 mg LUNESTA and 1.4% of 7.2 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 5-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 2 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergen adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2

adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are limited to adverse events that occurred in 2% or more of patients treated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients teated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients treated with LUNESTA 2 mg (n=104), which is a subject to the state of the incidence in placebo-treated patients (n=99). Body as a whole; headache (13%, 21%, 17%), viral infection (1%, 3%, 3%), bigostive system; dry mount (3%, 5%, 7%, 5%, persia, 14%, 4%, 5%, 4ms, 5%), annual since (3%, 6%, 3%), depression (0%, 4%, 4%, 3%), libido decreased (9%, 0%, 3%), nervousness (3%, 5%, 9%), somnolence (3%, 10%, 8%). Respiratory system; infection (3%, 5%, 6%), somnolence (3%, 10%, 8%). Respiratory system; infection (3%, 5%, 6%), system appendagus, rash (1%, 3%, 4%). Sperial senses; unpleasant taste (3%, 17%, 34%). Limantial system; of the missing decreased (3%, 6%), openconasta* (0%, 3%, 0%), dependagus, rash (1%, 3%, 4%). Sperial senses; unpleasant taste (3%, 17%, 34%). Limantial system; of the missing decreased (3%, 6%), openconasta* (0%, 3%, 0%), dependagus, rash (1%, 3%, 1%), or in females

*Gender-specific adverse event in females

Exposure of a developing brain to alcohol 'Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis. Advarse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

The following lists the incidence (% placeb, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LNRSTA at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more of patients treated with LUNESTA in mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.

patients!

Body as a whole; accidental injury (1% 0% 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Dinestive system; diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dryspensia (2%, 6%, 2%). Arrous system; abnormal dreams (9%, 3%, 1%), dryspensia (2%, 6%, 2%). Arrous system; abnormal dreams (9%, 3%, 1%), dryspensia (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%), Skin and appendance; pruritus: (1%, 4%, 1%). Special senses; unpleasant taste (0%, 8%, 12%), uropenital system; urinary tract infection (0%, 3%, 0%).

Events for which the LUNESTA incidence was equal to or less than piacebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Sommoneroe.

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevalled in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

regations involving uniferent iteatments, uses, and investigations.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

event incidence rate in the population studied.

Other Events Observed During The Premarketing Evaluation Of LUNESTA.
Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section and reported by approximately 1590 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listledner or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-rested. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.
Events are listed in order of decreasing frequency according to the following definitions: frequent adverse events are those that occurred on patients, infrequent adverse events are those that occurred in fewer than 17.00 patients, because the second on their incidence for the appropriate gender.

Frequent chear pain, migraine, peripheral edema.

Infrequent: carne, agritation, allergic reaction, allopecia, inmenorrhea, anemia, anorexia,

Frequent: chest pain, migraine, peripheral edima.

Infrequent: acne, apitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, artificis, asthma, atasia, breast enporgement, breast enlargement, breast neoplasm, breast pain, bronchitis, burstis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystistis, orly eyes, dry skin, dysprea, dyspuria, eczema, ear piain, emotional lability, epistaxis, face edema, fornale lactation, fever, haitosis, heat stroke, hematuria, hernia, hiccue, hostiliti, hypercholesterenia, hypertension, hyperthesia, incoordination, increased appetite, insornia, joint disorder (mainly, swelling, stiffness, and pein), kidney calculus, kidney pani, lanyingtis, leig cramps, lymphadenopathy, malaise, mastitis, melena, memory impairment, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, nyslagmus, otitis externa, otitis media, peresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, linnitus, twitching, ulberative stomatitis, urnary frequency, urinary incontinence, uritaria, uterine hemorrhage, vaginal hemorrhage, vaginits, vertigo, vestibular disorder, welght gain, weight loss.

Rare: abnormal gait, arthrosis, colitis, delydration, dysphagia, erythema multiforme, euphoria, frunculosis, gastritis, gout, hepatitis, hepatimengaly, herpas zoster, hirsutism, hyperacusis, hyperesthesia, hyperfipemia, hypokalemia, typokinesia, stuport, thornobophiebitis, tongue edema, tremor, urethritis, vesticulobullous rasti.

PRUS ABUSE AND DEPENDENCE

vesiculobullous rash.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: LUNESTA is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepine historyadiazepine hypotolics zaleplon and zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

Abuse, Dependence, and Tolerance
Abuse and Dependence: In a study of abuse liability conducted in individuals with
known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses reports of amnesia and hallucinations was observed for hoth LUNESTA and diazepam. The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hyprotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and curation of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnoric

LUNESTA or any other hypnotic. Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzo-diazepine-like agents may develop after repeated use of these drugs for a few weeks No development of follerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA'S mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep main-tenance for LUNESTA' in a placebo-controlled 4-day skudy, and by subjective assess-ments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

overnous at time to steep oriset and viscou in a pieceor-various assay or a memory overnous. The provided is a provided in the state of verdoes with the effects of an overdosage of DIMESTA. In clinical trials with escopicione, one case of overdoes with up to 35 mg of escapicione was reported in which the subject fully recovered. Individuals have fully recovered from racenic zopicione overdoses up to 340 mg (56 times the maximum recommended dose of escopicione).

maximum recommended dose of eszopicione). Signs And Symptons: Signs and symptons of overdise effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racernic zopicione have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents. Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gestric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug considers precipition values blood pressure and other ammorriate signs should be

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. The value of dialysis in the treatment of overdosage has not been determined.

value or dialysis in the treatment of overtiosage has not used determined. Prison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

