Eating Disorders Common in Girls With Diabetes

BY KATE JOHNSON

Montreal Bureau

MONTREAL — Eating disorders occur twice as often in adolescent girls and young women with type 1 diabetes mellitus, compared with their nondiabetic peers, and prepubertal diabetic girls should be screened for these disorders routinely, experts said at an international conference sponsored by the Academy for Eating Disorders.

Studies show that full-syndrome eating disorders are present in 10%, and subthreshold disorders in 14%, of adolescent girls with diabetes, compared with 4% and 8%, respectively, in healthy age-matched controls, said Patricia Colton, M.D., of the University of Toronto. Her own work in diabetic girls aged 9-14 years found an 8% prevalence of subthreshold eating disorders, compared with 1% in nondiabetic controls (Diabetes Care 2004;27:1654-9).

Such disturbed eating has been linked

with poor metabolic control and increased rates of diabetes-related complicationsin particular, a threefold risk of diabetic retinopathy, she said. Thus, early detection and treatment of eating disorders can have long-term benefits.

It has been suggested that a collection of multiple, interacting factors contributes to the development of eating disorders in patients with diabetes, Dr. Colton said.

Before their diagnosis, many diabetic girls tend to lose weight, which can often return to above baseline after treatment begins. Insulin therapy can cause weight gain, particularly during puberty, and episodes of hypoglycemia, so common in diabetes, can trigger binge eating, which has been reported in 45%-80% of women with diabetes. "Low blood sugar is an incredibly strong biological trigger to eat," she noted.

All these factors may contribute to feelings of body dissatisfaction and efforts to control weight, including one method unique to diabetes—the omission of insulin therapy, reported by 12%-40% of this population.

But overlying these concerns are such daily management concerns as self-monitoring, dietary restraint, and preoccupation with food, which can give rise to issues of control and rebellion, especially in the adolescent population, she said.

'Dealing with a chronic medical condition can have significant effects on the child and the family. Depression and anxiety disorders are doubled or tripled in individuals with diabetes," she said, adding that depressive symptoms have also been linked with hyperglycemia.

Established treatments for eating disorders appear effective in patients with diabetes, but tailoring these treatments more closely to diabetes-specific issues may enhance their value for this population, said Marion Olmsted, Ph.D., who is also with the University of Toronto and is director of ambulatory care for eating disorders at the University Health Network, Toronto General Hospital.

Psychoeducational interventions can improve weight and body-shape attitudes in teenaged girls who do not have fullblown eating disorders. Cognitive-behavioral strategies can be used to address issues such as blood sugar monitoring, insulin underdosing or omission, and eating patterns. And psychotherapy can address issues of rebellion, control, anger, and depression. More intensive approaches, such as day hospital treatment, are required in some cases, she explained.

Research by Dr. Olmsted and her colleagues at the University of Toronto has shown that diabetic girls with eating disturbances report less support, poorer communication, and less trust in their relationships with their parents than do diabetic girls without eating disturbances (J. Psychosom. Res. 1998;44:479-90).

In one study, mothers who were videotaped interacting with their daughters who had diabetes and eating disturbances showed less empathy, affective engagement, and support for their child's age-appropriate autonomy, compared with mothers of diabetic daughters without eating disturbances (J. Consult Clin. Psychol. 2001;69:950-8).

"Mothers of diabetic girls with eating disturbances appear to be less able to balance their teenage daughters' complementary needs for independence and supportive guidance," Dr. Olmsted and her associates said in a literature review (J. Psychosom. Res. 2002;53:943-9).

Evidence shows that as adolescence progresses, behaviors such as insulin omission and binge eating become more common in young women, they reported.



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 maintenance.

WARNINGS

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 lineas 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/hypontic drags, including LUNESTA. Because some of the important adverse effects of LUNESTA 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).

ThatToN in the Full Prescribing Information.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedature/hypnotics. 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 depressents. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Annessa 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 sedature/hypnotics.

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

bindering psychiatric or gnysteal disorder. Morteureses, the entergetice of any few behavioral sign or symptom of concern requires careful and immediate evaluation. Following rapid dose decrease or abrupt discontinuation of the use of sedative/hyportics, there have been reports of signs and symptoms similar to those associated in whith withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE). LINESTA, like other hyportics, has CNS-depressant effects. 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 saleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be autioned about potential impairment of the performance of such advitises on the day following ingestion of LUNESTA, LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antificatamines, ethanol, and other drugs that themselves produce CNS depression, LUNESTA should not be taken with alchol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS

General

Timing 01 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, dizziness, and lightheadedness.

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 elderly 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 Illness: Clinical experience with eszopiclone in patients with concomitant illness is imited. Eszopiclone should be used with caution in patients with ocnocomitant illness is imited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

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 excopicione. Caution is advised, 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 mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of exceptione is excreted unchanged in the urine.

since less than 10% of exceptione is excreted unchanged in the urine. The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYP3A4, 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: Settive/hypnotic drugs should be administered with audition to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intertional overdose is more common in this group of patients; therefore, the state 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

Ethanol: An additive effect on psychomotor performance was seen with coadministra-tion of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration. Paroxetine: Coadministration of single dosses of eszopiclone 3 mg and paroxetine 20 mg daily to r 7 days produced no pharmacokinetic or pharmacodynamic interaction.

2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of etither drug.

**Olanzapine: Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a
decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

**Drugs That Inhibit CYP3A4 (Retoconazole): CYP3A4 is a major metabolic pathway for
elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400, mg daily for 5 days.

**Creamant Ly were increased 1.4-fold and 1.3-fold, respectively. One's strong inhibitors

of CYP3A4 (e.g., triaconazole, clarithromycin, nefazodone, troleandomycin, ritonavir,
nefinean'y would be expected to be behave similar, respectively. One's strong inhibitors

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nefinean'y would be expected to be behave similar effect would be expected to be have similar effect would be expected with eszopiclone.

**Drugs Highly Bound To Plasma Protein: Eszopiclone is not highly bound to plasma
proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected

to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg

to a patient taking another drug that is highly protein-bound washing and the drug that is highly protein-bound washing another drug that is highly protein-bound washing and the drug that is highly because the service of the protein that the

Drugs With A Narrow Therapeutic Index
Narrow Therapeutic Index
Warfarin: Escopicione 3 mg administered daily for 5 days did not affect the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.
Carcinogenesis: Indagenesis. Impairment of Fertility
Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which escopicione was given by oral gavage, no increases in tumors were seen; plasma levels
(AUC) of escopicione at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (temales) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in

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 pland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in females were seen at the highest dose of 100 mg/kg/dga, Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans is unknown. The increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased matabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C8F1 mice in which racemic zopiclone was given in the diet, an increase in planmary 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 MRHD. 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 gavages those in humans receiving the MRHD. The pulmonary or skin tumors were seen at doses producing plasma levids of eszopiclone ed more skin tumors were seen at doses producing plasma levids of eszopiclone defined to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral deseau but 200 mg/kg/day.

szopiclone did not increase tumors in a p53 transgenic mouse bioassay al oral sees up to 300 mg/kg/day.

doses up to 300 mg/kg/day.

Mutagenesis: Eszopicione 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 Arnes gene mutation assay, it man on the theoretical Arnes gene mutation assay, in an unscheduled DNA synthesis assay, or in an in vivo mouse bone macrow micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an in vitro 32P-postlabeling DNA adduct assay, and in an in vivo mouse bone marrow chromosomal aberration and micronucleus assay.

adultic assay, and in an interventional control and assay, and in an interventional micronucleus assay.

Impairment Of Fertifity Eszopicione was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 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 fertifity, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 tines the MRHD on a mg/m² basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), ahornmal estrus cycles (no-effect dose 25 mg/kg), and decreases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

phologically amounted seem (no-effect dose 5 mg/kg).

Pregnancy Zebgory C: Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively; these doses are 300 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis). In the rat, signit reductions in fetal veight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m² basis). Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day, Increased post-implantation loss, decreased postantal pure veights and survival; and increased post-implantation loss, decreased postantal pure veights and survival; and increased post-implantation loss, decreased postantal pure veights and survival; and increased post-implantation in engine basis. These doses did not produce significant maternal toxicity, Eszopiclone had no effects on other behavioral measures or reproduct function in the offspring.

There are no adequate and well-controlled studies of eszopiclone in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefit justifies the potential first to the fether of the three presents and the potential benefit justifies the potential maternal through the potential benefit in the maran milk.

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 eszopicione in children below the age of 18 have not been established.

nave not been established.

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopicione were 65 to 66 years of age. The overall pattern of adverse events for elderly subjects (median age — 71 years) in 2-week
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 elderly population.

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ADVERSE REACTIONS

The premarkating development program for LUNESTA included escopicion exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 2650 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, vital signs, weights, laboratory analyses, and ECGs.

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 represent the proportion of individuals experiencing adverse events represent the proportion of individuals experiencing adverse events represent the proportion of individuals who experienced, at least once, a 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 placebo, 2.3% of 215 patients who received placebo and 12.8% of 539 patients who received a nativerse event. In the 6-week parallel-group clinical trials in the elderly cerement forment of an adv

resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Disserved at an Incidence of 22% in Controlled Trials. The following lists the incidence (%) placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-eldedry 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 placebo-treated patients treated with LUNESTA as greater than the incidence in placebo-treated patients treated with LUNESTA was greater than the incidence in placebo-treated patients (re-99). Body as a whole; headache (13%, 21%, 17%), viral infection (1%, 3%, 3%), 80, 95%), espensia (4%, 4%, 5%), nausea (4%, 5%, 4%), vornting (1%, 3%, 6%), 6%), Sepresia (4%, 4%, 5%), inausea (4%, 5%, 4%), vornting (1%, 3%, 6%), 6%), espension (0%, 4%, 4%, 5%), inausea (4%, 5%, 4%), somnolence (3%, 10%, 3%), depression (0%, 4%, 4%), increased (3%, 5%, 0%), sepression (3%, 4%, 4%), increased (3%, 17%, 34%), limaential system: and appendages; rash (1%, 3%, 4%), Secial senses; unpleasant taste (3%, 17%, 34%), limaential system: developed (3%, 5%, 0%), depression developed (3%, 5%, 0%), grecomasta** (6%, 3%, 0%), defender-specific adverse event in females

'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, dizzness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste. With this relationship clearest for unpleasant taste, with this relationship clearest for moleoned Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (agues 65-68). 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 ordered.

listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

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 prevailed in the clinical trials. Similarly, the clied frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

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.

Other Events Observed During The Premarketling Evaluation Of LUNESTA. Allowing 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 1550 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 listed here or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. 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 definions: frequent adverse events are those that occurred in fewer than 171.000 patients; rare adverse events are those that occurred in fewer than 171.000 patients, rare adverse events are those that occurred in fewer than 171.000 patients, such appropriated, although the events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migrain

posed on their incidence for the appropriate gender.

Frequent, chest pain, migrafile, perioberal edema.

Infrequent: acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, attrific, asthma, attaui, breast engogenemit, breast enlargement, breast enlargement

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 substances and the nonbearcodiazepine 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.

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Abusa, Dependence, and Tolerance

Abusa, 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 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both LUNESTA and diazepam. The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following advarse events included in DSM-IV criteria for uncomplicated scatchievelynoprior windrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal direams, nausea, and upset stormach. These reported advarse 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 duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or ding abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving 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 onzepnie-like agents may develop anter repeated use or inseed triggs for a few weeks. No development of follerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA3 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 study, and by subjective assess-ments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

OVERDOSAGE
There is limited premarketing clinical experience with the effects of an overdosage of LUNESTA. In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Individuals have fully recovered from racemic zopiclone overdoses up to 340 mg (56 times the maximum recommended dose of eszopiclone).

maximum recommended dose of eszopicione).

Signs And Symptoms: Signs and symptoms of overdose 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 come has been described. Rare individual instances of fatal outcomes following overdose with racemic topoletion have been reported in Europeen 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 gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenli may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be uncitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate melatine trevention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The value of dialysis in the treatment of overdosage has not be endeal intervention. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypotectic drug product overdosage.

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