FDA Seeks to Increase Fees for Drug Makers

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The Food and Drug Administration has proposed greatly increasing the fees its drug division collects from pharmaceutical manufacturers, saying that current fees collected under the Prescription Drug User Fee Act have not kept pace with inflation or the agency's growing workload.

Most of the additional money would be used to upgrade the agency's postmarketing drug safety monitoring. The FDA also is proposing to create a separate program to collect fees from companies that want their direct-to-consumer television ads reviewed by the agency.

The FDA published its proposals in the Jan. 11 Federal Register and will collect comments on them at a public meeting on Feb. 16. The final proposal will be sent to Congress later this year, said Jane Axelrad, associate director for policy at the Center for Drug Evaluation and Research (CDER), in a teleconference sponsored by the FDA.

Time is of the essence, as PDUFA—first established in 1992 and reauthorized in 5-year increments—is due to expire on Sept. 30, 2007.

Under PDUFA, the FDA charges prescription drug makers a set fee to review the safety and efficacy of products submitted under a new drug application. In return, the agency has to meet deadlines for review and approval.

The law has helped the FDA to reduce review times and increase its postmarketing oversight, said Dr. Steven K. Galson, CDER director, during the teleconference.

Under the new proposal, FDA seeks to collect $393 million annually, $87 million more than it currently takes in each year. Drug user fees account for about half of CDER's budget, said Dr. Galson, adding that he could not say whether that would hold true going forward, since the agency has not yet received its appropriation for fiscal 2007 or a budget for fiscal 2008.

However, Ms. Axelrad said that drug user fees represent an increasing proportion of CDER's budget.

Public Citizen's Health Research Group criticized that trend, saying that the agency should not receive so much of its funding from the industry it regulates.

"The FDA's crucial drug regulatory functions are too important to be tainted and compromised by direct funding from the very companies whose drugs the agency reviews for safety," said Dr. Sidney Wolfe, director of the advocacy group, in a statement.

The biotechnology and pharmaceutical industries praised the FDA proposal. "The PDUFA recommendations announced today … will help enhance and improve drug safety while providing resources to continue to enable efficient and comprehensive review of new drugs," said Jim Greenwood, president and CEO of the Biotechnology Industry Organization, in a statement.

The largest portion of the increase, $29 million, would be devoted to postmarketing safety. With those funds, the agency said it could hire 82 new employees and acquire the best tools for improving detection and analysis of safety signals. The agency also will institute new programs to reduce medication errors, in response to an Institute of Medicine report issued in September 2006 calling for drug safety improvements at the agency.

Some $20 million would go to cover past expenses incurred to facilitate drug makers' requests for formal meetings about their products. Sheila Mullin, FDA assistant commissioner for planning, said that in fiscal 2005, the agency held 1,800 formal meetings at manufacturers' request.

About $4 million would be devoted to the goal of moving to "an all-electronic environment," according to the FDA proposal.

"Reviewing data electronically helps to improve the efficiency of the drug approval process and expedites getting important new drugs to the patients who need them," said Billy Tauzin, president and CEO of the Pharmaceutical Research and Manufacturers of America, in a statement.

FDA is proposing to create a new user fee program to fund the review of direct-to-consumer television ads. Currently, companies can voluntarily submit ads for review, but the FDA has not been able to keep up with the growing workload, Dr. Galson said. The FDA anticipates charging $6 million in the first year of the program, which would subsidize the hiring of 27 new employees. Another $6 million would be collected for a reserve fund, to cope with increases in volume of advertisements. ■

Lunesta®
(eszopiclone)c
1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

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.

CONTRAINDICATIONS
None known.

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 illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including 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, especially in the elderly (see **DOSAGE AND ADMINISTRATION 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/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 depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia 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/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. 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/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**).

LUNESTA, like other hypnotics, 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 falling asleep. 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 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, anticonvulsants, antihistamines, ethanol, and other drugs that themselves 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.

PRECAUTIONS
General

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, 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 limited. Eszopiclone 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 eszopiclone. 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 eszopiclone 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: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and 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 in the complete prescribing information.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS-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 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 (Ketoconazole): 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. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A4 (Rifampicin): Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A 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 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 eszopiclone 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.

Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) 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 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 is unknown. The increase in thyroid tumors 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 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 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 gavage; 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—i.e., 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.

Mutagenesis: Eszopiclone 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 hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment Of Fertility: Eszopiclone 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. Eszopiclone decreased fertility, 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 times the MRHD on a mg/m^2 basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy
Pregnancy Category 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 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). In the rat, slight reductions in fetal weight 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/m^2 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 postimplantation loss, decreased postnatal pup weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m^2 basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive 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 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 have not been established.

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 86 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 eszopiclone 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.

ADVERSE REACTIONS
The premarketing development program for LUNESTA included eszopiclone 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 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, 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 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 placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-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 3 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-emergent 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 treated with LUNESTA was greater than the incidence in placebo-treated patients (n=99).[1]

Body as a whole: headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). Digestive system: dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), vomiting (1%, 3%, 0%). Nervous system: anxiety (0%, 3%, 1%), confusion (0%, 0%, 3%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), libido decreased (0%, 0%, 3%), nervousness (3%, 5%, 0%), somnolence (3%, 10%, 8%). Respiratory system: infection (3%, 5%, 10%). Skin and appendages: rash (1%, 3%, 4%). Special senses: unpleasant taste (3%, 17%, 34%). Urogenital system: dysmenorrhea* (0%, 3%, 0%), gynecomastia** (0%, 3%, 0%).

*Gender-specific adverse event in females

**Gender-specific adverse event in males

[1]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.

Adverse 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 (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA 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 1 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.[1]

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%). Nervous system: abnormal dreams (0%, 3%, 1%), dizziness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%). Skin and appendages: pruritus: (1%, 4%, 1%). Special senses: unpleasant taste (0%, 8%, 12%). Urogenital system: urinary tract infection (0%, 3%, 0%).

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not 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 cited 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 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 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 definitions: **frequent** adverse events are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse events are those that occurred in fewer than 1/1,000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

Infrequent: acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast neoplasm, breast pain, bronchitis, bursitis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystitis, dry eyes, dry skin, dyspnea, dysuria, eczema, ear pain, emotional lability, epistaxis, face edema, female lactation, fever, halitosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesteremia, hypertension, hypertonia, hypesthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastitis, melena, memory impairment, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, nystagmus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, tinnitus, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

Rare: abnormal gait, arthrosis, colitis, dehydration, dysphagia, erythema multiforme, euphoria, furunculosis, gastritis, gout, hepatitis, hepatomegaly, herpes zoster, hirsutism, hyperacusis, hyperesthesia, hyperlipemia, hypokalemia, hypokinesia, iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy, oliguria, photophobia, ptosis, pyelonephritis, rectal hemorrhage, stomach ulcer, stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis, 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 benzodiazepines and the nonbenzodiazepine hypnotics 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 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 adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic 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 duration 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 hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks.

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 44-day study, and by subjective assessments 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).

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 coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone 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 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. The value of dialysis in the treatment of overdosage has not been determined.

Poison 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.

Rx only.

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