PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLUNESTA®

Eszopiclone Tablets, USP

1 mg, 2 mg, and 3 mg, Oral

Hypnotic Agent

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PrLUNESTA®
Eszopiclone tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	1 mg, 2 mg, and 3 mg	Tablets: Colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate dihydrate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose. Film-coat: Opadry® blue (1 mg only), Opadry® white (2 mg only), Opadry® blue (3 mg only).

INDICATIONS AND CLINICAL USE

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient.

Adults:

LUNESTA (eszopiclone) is indicated for the short-term treatment and symptomatic relief of insomnia including difficulty falling asleep, nocturnal awakenings or early morning awakenings.

Treatment with LUNESTA should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for LUNESTA should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.

Geriatrics (> 65 years of age):
There is a risk for greater sensitivity to the drug effects in the elderly [see also **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**]. A lower maximum dose is recommended in the elderly (see **DOSAGE AND ADMINISTRATION**, **Special Populations**, **Geriatrics**).

Pediatrics (< 18 years of age):
Safety and efficacy of eszopiclone in children below the age of 18 have not been established. [see also **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (<18 years of age)**].

CONTRAINDICATIONS

LUNESTA (eszopiclone) is contraindicated in:

- Patients who are hypersensitive to this drug or to zopiclone (marketed in Canada as IMOVANE), or to any ingredient in the formulation or component of the container. Observed reactions to eszopiclone have included angioedema and anaphylaxis (see **WARNINGS AND PRECAUTIONS**, **Hypersensitivity**). For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Patients with myasthenia gravis.
- Severe respiratory impairment (e.g., significant sleep apnea syndrome).
- Elderly patients receiving concomitant potent CYP3A4 inhibitors or having severe hepatic insufficiency.
- Patients who have experienced complex sleep-related behaviours after taking LUNESTA or any other hypnotic agent (see boxed **SERIOUS WARNINGS AND PRECAUTIONS: COMPLEX SLEEP-RELATED BEHAVIOURS**)

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

COMPLEX SLEEP-RELATED BEHAVIOURS: Complex sleep-related behaviours including sleep-walking, sleep-driving, and engaging in other potentially dangerous activities while not fully awake may occur following use with LUNESTA. Some of these events may result in serious injuries, including death to self or others. Patients usually do not remember these events. Although complex sleep-related behaviours may occur with LUNESTA alone at therapeutic doses, the use of alcohol and other CNS-depressants with LUNESTA appears to increase the risk of such behaviours, as does the use of LUNESTA at doses exceeding the maximum recommended dose. Discontinue LUNESTA immediately if a patient experiences a complex sleep-related behaviour (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Complex Sleep-related Behaviours**).

- LUNESTA is not to be taken with alcohol
- Caution is needed with concomitant use of other CNS-depressants (see **DRUG INTERACTIONS**).
- The use of LUNESTA in patients with other disorders known to affect sleep and induce frequent awakenings (e.g. sleep apnea, Periodic Limb Movement Disorder, Restless Legs Syndrome) is discouraged, as they may be also at increased risk of complex sleep-related behaviours
- Continuous use of LUNESTA is limited to a short duration (see **INDICATIONS AND CLINICAL USE**, **DOSAGE AND ADMINISTRATION**).
- Patients should be instructed not to exceed the recommended dose
- Caution should be exercised with concomitant use of potent CYP3A4 inhibitors (see **DRUG INTERACTIONS**).

RISKS FROM CONCOMITANT USE WITH OPIOIDS: Concomitant use of LUNESTA

and opioids may result in profound sedation, respiratory depression, coma, and death (see **WARNINGS AND PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines or other CNS depressants**).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

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 to identify the underlying cause whenever possible. **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 behaviour abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sleep-inducing drugs, including LUNESTA (eszopiclone).

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. Inappropriate, heavy sedation in the elderly, may result in accidental events including falls. The use of the lowest effective dose is also consistent with management of other dose-related risks associated with eszopiclone (see boxed **SERIOUS WARNINGS AND PRECAUTIONS: COMPLEX SLEEP-RELATED BEHAVIOURS**, **WARNINGS AND PRECAUTIONS, Neurologic**, **Amnesia, Complex Sleep-related Behaviours, CNS Depressant Effects and Next-Day Impairment, Drug Abuse, Dependence and Withdrawal**).

LUNESTA should be taken immediately before bedtime. Taking a hypnotic agent while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness (see **WARNINGS AND PRECAUTIONS**, **Neurologic, Psychiatric**).

Benzodiazepines and benzodiazepine-like agents are to be used with extreme caution in patients with a history of alcohol or substance abuse.

CNS Depressant Effects and Next-Day Impairment

Like other sedative/hypnotic drugs, LUNESTA has CNS-depressant effects. Due to the rapid onset of action, LUNESTA should be ingested **immediately prior to going to bed.**

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug.

This includes potential impairment of the performance of such activities that may occur the day following ingestion of LUNESTA. The risk of next day psychomotor impairment, including impaired driving, is increased if LUNESTA is taken with less than a full night of sleep

remaining; if a higher dose than the recommended dose is taken; if co-administered with other CNS depressants; if co-administered with other drugs that increase the blood level of eszopiclone or in patients with severe hepatic impairment. Patients should be cautioned against taking LUNESTA in these circumstances.

Because LUNESTA can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

The lowest effective dose for the patient should be used.

LUNESTA is not to be taken with alcohol or other sedative hypnotics at bedtime or the middle of the night. If concomitant use of another CNS depressant or a drug that increases eszopiclone blood levels is clinically warranted, dosage adjustments of LUNESTA may be necessary.

Even if LUNESTA is taken as instructed, some patients may still have eszopiclone blood levels in the morning high enough to produce impairment (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

Patient counseling information regarding next-day impairment: Tell patients that LUNESTA has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients not to drive a car or engage in hazardous activities requiring complete alertness until they experience how the drug affects them the next day. Tell patients that if they took LUNESTA as instructed and do not feel drowsy in the morning, they still have to wait for at least 12 hours after dosing before driving or engaging in other activities requiring full mental alertness, especially for elderly patients, patients with severe hepatic impairment and for patients who take the 3 mg dose. Inform patients that impairment can be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.

Complex Sleep-related Behaviours

Complex sleep-related behaviours including sleep-walking, sleep-driving, and engaging in other potentially dangerous activities while not fully awake may occur following the first or any subsequent use of LUNESTA. Patients may seriously injure themselves or others during complex sleep-related behaviours. Fatal outcomes have been reported. Other complex sleep-related behaviours (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Post-marketing reports have shown that complex sleep-related behaviours may occur with LUNESTA alone at recommended doses, with or without the concomitant use of alcohol or other CNS-depressants (see **DRUG INTERACTIONS**). However, when taken together, alcohol or CNS depressants may increase the risk of such behaviours, as does the use of LUNESTA at doses exceeding the maximum recommended dose. Discontinue LUNESTA immediately if a patient experiences a complex sleep-related behaviour.

LUNESTA is not to be taken with alcohol.

Caution is needed with concomitant use of other CNS depressants drugs.

Caution is recommended in patients with a personal or family history of sleepwalking. Although complex sleep-related behaviours have been reported in patients with or without history of sleepwalking, it is possible that some predisposed patients are at increased risk of experiencing these complex behaviours during treatment with LUNESTA.

The use of LUNESTA in patients with other disorders known to affect sleep and induce frequent awakenings (e.g. sleep apnea, Periodic Limb Movement Disorder, Restless Legs Syndrome) is discouraged, as they may be also at increased risk of complex sleep-related behaviours.

Treatment with LUNESTA is limited to a short duration (see **INDICATIONS AND CLINICAL USE**, **DOSAGE AND ADMINISTRATION**).

Patients should be instructed not to exceed the recommended dose.

Caution should be exercised with concomitant use of potent CYP3A4 inhibitors (see **DRUG INTERACTIONS**).

Risks from concomitant use of opioids and benzodiazepines or other CNS depressants
Concurrent use of LUNESTA with opioids, benzodiazepines, or other CNS depressants may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If a decision is made to prescribe LUNESTA concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of LUNESTA than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking LUNESTA, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see **DRUG INTERACTIONS**).

Advise both patients and caregivers about the risks of respiratory depression and sedation when LUNESTA is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined (see boxed **SERIOUS WARNINGS AND PRECAUTIONS: RISKS FROM CONCOMITANT USE WITH OPIOIDS**, and **WARNINGS AND PRECAUTIONS, CNS Depressant Effects and Next-Day Impairment**).

Drug Abuse, Dependence and Tolerance

As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

Abuse

Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

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. Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse, and addiction to LUNESTA, they should be monitored carefully when receiving LUNESTA.

Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.

Use of benzodiazepines and benzodiazepine-like substances may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or history of addiction to, or abuse of, drugs or alcohol.

If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms which may include headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or seizures.

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 **ADVERSE REACTIONS, Withdrawal Events**).

Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

In clinical studies with LUNESTA, no development of tolerance to any median parameter of sleep measurements was observed during treatment periods of up to 12 months. Development of tolerance in some patients cannot be excluded.

Rebound Insomnia
A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Rebound insomnia manifested as an increase in sleep latency for one to two nights has been observed following cessation of LUNESTA treatment. These events resolved without intervention. It is important that patients be aware of the possibility of rebound phenomena, thereby minimising anxiety should such symptoms develop when the medicinal product is discontinued.

Hypersensitivity

Severe Anaphylactic and Anaphylactoid Reactions
Rare cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of a sleep-inducing agent, including LUNESTA. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with LUNESTA should not be rechallenged with the drug.

Neurologic

Amnesia
Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines or benzodiazepine-like agents. The event is rare with LUNESTA. Anterograde amnesia is more likely to occur when sleep is interrupted or when retiring to bed is delayed after intake of the tablet. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Cases of transient global amnesia and “traveler’s amnesia” have also been reported in association with benzodiazepines, the latter in individuals who have taken the drug, often in the middle of the night, to induce sleep while travelling. Transient global amnesia and traveler’s amnesia are unpredictable and not necessarily dose-related phenomena.

To reduce the possibility of anterograde amnesia, patients should ensure that they take the tablet strictly when retiring for the night. Patients should be warned not to take LUNESTA under circumstances in which a full night’s sleep and clearance of the drug from the body are not possible before they need again to resume full activity.

Psychomotor Impairment
Benzodiazepines and benzodiazepine-like agents may induce psychomotor impairment, including accidental injury and falls. In particular, elderly patients may be more vulnerable to falls resulting in injuries such as hip fractures. Psychomotor impairment most often occurs several hours after ingesting the product and therefore patients are to ensure they will have an uninterrupted sleep period of 7-8 hours (see also **WARNINGS AND PRECAUTIONS**, **CNS Depressant Effects and Next-Day Impairment**, and **Special Populations**, **Geriatrics**).

Cognitive Function
Benzodiazepines and benzodiazepine-like compounds may affect concentration, attention and vigilance. This risk is greater in the elderly and in patients with cerebral impairment.

Psychiatric

Anxiety, restlessness
An increase in daytime anxiety and/or restlessness have been observed during treatment with LUNESTA. This may be a manifestation of interdose withdrawal, due to the short elimination half-life of the drug.

Abnormal Thinking and Behavioural Changes
Reactions like restlessness, aggravated insomnia, agitation, irritability, aggressiveness, delusion, rages, nightmares, parasomnia, depersonalization, hallucinations, psychoses, inappropriate behaviour, and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like agents. They may be drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines or benzodiazepine-like agents. These reactions are more likely to occur in the elderly. If this occurs, discontinuation of LUNESTA is to be considered until further evaluation. Any new behavioural sign or symptom requires careful and immediate evaluation.

Depression
In primary depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported in association with the use of sedative/hypnotics. Benzodiazepines and benzodiazepine-like agents are not to be used alone to treat patients with depression or anxiety associated with depression (suicide may be precipitated in such patients). These agents should be administered with caution to patients exhibiting signs and symptoms of depression. Intentional overdose is more common in this group of patients and the least amount of drug that is feasible should be prescribed for the patient at any one time.

Respiratory

A study in healthy volunteers did not reveal respiratory-depressant effects at doses up to 7 mg (2.5-folds the maximum recommended dose). Since sedative/hypnotics have the capacity to depress respiratory drive, caution is advised if LUNESTA is prescribed to patients with compromised respiratory function.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. LUNESTA is not recommended during pregnancy and should be used only if the potential benefit justifies the potential risk to the fetus.

Oral administration of eszopiclone to pregnant rats (62.5, 125, or 250 mg/kg/day) and rabbits (4, 8, or 16 mg/kg/day) throughout organogenesis showed no evidence of teratogenicity up to the highest doses tested. In rats, reduced fetal weight and increased incidences of skeletal variations and/or delayed ossification were observed at the mid and high doses. The no-observed-effect dose for adverse effects on embryofetal development is 200 times the maximum recommended human dose (MRHD) of 3 mg/day on a mg/m^2 basis. No effects on embryofetal development were observed in rabbits; the highest dose tested is approximately 100 times the MRHD on a mg/m^2 basis.

Oral administration of eszopiclone (60, 120, or 180 mg/kg/day) to pregnant rats throughout the pregnancy and lactation resulted in increased post-implantation loss, decreased postnatal pup weights and survival, and increased pup startle response at all doses. The lowest dose tested is approximately 200 times the MRHD on a mg/m^2 basis. Eszopiclone had no effects on other developmental measures or reproductive function in the offspring.

Nursing Women: Animal and human studies have demonstrated transfer of racemic zopiclone into breast milk. It is not known whether LUNESTA is excreted in human milk. The excretion of eszopiclone in milk has not been studied in animals. Because many drugs are excreted in human milk, administration of LUNESTA to a nursing woman is not recommended.

Fertility: A human clinical study of adult males did not show any evidence of impaired fertility. In a human clinical study there were no observed changes in female menstrual cycling. Animal studies with eszopiclone demonstrated reduced male and female fertility at exposures considered to be sufficiently in excess of the maximum human exposure.

Hepatic Impairment: Eszopiclone exposure was increased 2-fold and elimination half-life was prolonged by 8 hours (from 6.7 hrs to 15.3 hrs) in patients with severe hepatic impairment compared with the healthy volunteers. The dose of LUNESTA should not exceed 2 mg in patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION**). No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment.

Renal Impairment: Compared with healthy subjects, subjects with severe renal impairment had an increase in eszopiclone exposure of 47%. The dose of LUNESTA in patients with severe renal impairment should not exceed 2 mg (see **DOSAGE AND ADMINISTRATION**). No dose adjustment is necessary for patients with mild-to-moderate renal impairment.

Pediatrics (<18 years of age): The safety and effectiveness of eszopiclone in children below the age of 18 have not been established. LUNESTA failed to demonstrate efficacy in controlled clinical studies of pediatric patients with insomnia associated with Attention Deficit/Hyperactivity Disorder (ADHD).

In a clinical study of patients aged 6-17 years with insomnia associated with ADHD (most of whom were using ADHD treatments), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events when LUNESTA was compared to placebo and included dysgeusia (9% vs. 1%), dizziness (6% vs. 2%), hallucinations (2% vs. 0%), and suicidal ideation (0.3% vs. 0%).

Geriatrics (> 65 years of age): Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to benzodiazepine and benzodiazepine-like drugs is a concern in the treatment of the elderly. Inappropriate, heavy sedation may result in accidental events/fall. Subjects 65 years and older had 41% higher exposure (AUC) and prolonged elimination of eszopiclone ($t_{½}$ approximately 9 hours) compared to non-elderly adults. The maximum nightly dose of LUNESTA must not exceed 2 mg in elderly patients. (see also **DOSAGE AND ADMINISTRATION**, **ACTION AND CLINICAL PHARMACOLOGY**, ***Special Populations and Conditions***, **Geriatrics**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 reaction. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse reaction. 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 reaction. No reaction that resulted in discontinuation occurred at a rate of greater than 2%.

The most frequently observed adverse events during these trials were expected from the known pharmacologic properties of eszopiclone. These include unpleasant taste (dysgeusia), dizziness, somnolence, and dry mouth. The overall incidence of serious adverse events was similar between treatment groups (placebo: 1.0 to 2.1%; eszopiclone: 1.2 to 2.3%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events reported in this section were reported from a total of 11 studies that enrolled just over 4400 subjects. These trials were conducted in patients with insomnia using nighttime administration of eszopiclone. Study duration ranged from short-term dosing (1-7 days) to 6 months, with doses ranging from 1 to 3 mg. Study populations included non-elderly adults with and without medical co-morbidities and elderly adults. Treatment emergent adverse events (TEAEs) include those events that occurred or worsened upon or after administration of the first dose of double-blind study medication.

Treatment Emergent Adverse Events in Placebo-Controlled Clinical Trials with Dosing up to 2 weeks in Elderly Subjects

The most frequently reported adverse events are summarized in Table 1.

Table 1. All Treatment Emergent Adverse Events with an Incidence >2% in Either Active Group[1] in the Pooled (2 Weeks) Studies in Elderly Subjects

BODY SYSTEM Preferred Term Subject n (%)	All TEAEs		
	Placebo (N=208)	ESZ 1 mg (N=72)	ESZ 2 mg (N=215)
AT LEAST ONE AE	91 (43.8)	29 (40.3)	100 (46.5)
BODY AS A WHOLE			
Headache	29 (13.9)	11 (15.3)	29 (13.5)
Pain	4 (1.9)	3 (4.2)	10 (4.7)
Accidental injury	2 (1.0)	0	6 (2.8)
DIGESTIVE			
Dry mouth	4 (1.9)	2 (2.8)	14 (6.5)
Diarrhoea	5 (2.4)	3 (4.2)	5 (2.3)
Dyspepsia	5 (2.4)	4 (5.6)	4 (1.9)
NERVOUS			
Somnolence	14 (6.7)	5 (6.9)	12 (5.6)
Dizziness	5 (2.4)	1 (1.4)	12 (5.6)
Nervousness	3 (1.4)	0	5 (2.3)
Abnormal dreams	1 (0.5)	2 (2.8)	2 (0.9)
Neuralgia	0	2 (2.8)	0
SKIN AND APPENDAGES			
Pruritus	3 (1.4)	3 (4.2)	3 (1.4)
Rash	5 (2.4)	0	5 (2.3)
SPECIAL SENSES			
Unpleasant taste	1 (0.5)	6 (8.3)	26 (12.1)
UROGENITAL SYSTEM			
Urinary tact	1 (0.5)	2 (2.8)	0

1: And more frequent in at least one active treatment group than the placebo group.
TEAE=treatment emergent adverse event; ESZ=eszopiclone
COSTART Coding, ITT Population

The overall incidence of treatment-emergent adverse events (TEAE) was similar in placebo-treated and eszopiclone 1 mg and 2 mg-treated subjects at 43.8%, 40.3%, and 46.5%, respectively. Although not considered potentially related by the investigators, accidental injury was more prevalent among 2 mg eszopiclone-treated subjects than placebo-treated subjects (1.0% and 2.8%).

Treatment Emergent Adverse Events in a Placebo-Controlled Clinical Trial with 6 weeks Dosing in Non-Elderly Adults

The most frequently reported adverse events are summarized in Table 2.

Table 2. All Treatment Emergent Adverse Events with an Incidence >2% in Either Active Group[1] in a 6 Week Study in Non-Elderly Adults

BODY SYSTEM Preferred Term Subject n (%)	All TEAEs		
	Placebo (N=99)	ESZ 2 mg (N=104)	ESZ 3 mg (N=105)
OVERALL	51 (51.5)	69 (66.3)	74 (70.5)
BODY AS A WHOLE			
Accidental injury	5 (5.1)	3 (2.9)	7 (6.7)
Headache	12 (12.1)	20 (19.2)	17 (16.2)
Infection	3 (3.0)	5 (4.8)	11 (10.5)
Viral infection	1 (1.0)	3 (2.9)	3 (2.9)
DIGESTIVE			
Dry mouth	3 (3.0)	5 (4.8)	6 (5.7)
Dyspepsia	4 (4.0)	4 (3.8)	5 (4.8)
Nausea	4 (4.0)	5 (4.8)	4 (3.8)
Vomiting	1 (1.0)	3 (2.9)	0
NERVOUS			
Abnormal dreams	2 (2.0)	3 (2.9)	2 (1.9)
Anxiety	0	3 (2.9)	1 (1.0)
Depression	0	4 (3.8)	1 (1.0)
Dizziness	4 (4.0)	5 (4.8)	6 (5.7)
Hallucinations	0	1 (1.0)	3 (2.9)
Libido decreased	0	0	3 (2.9)
Nervousness	2 (2.0)	5 (4.8)	0
Somnolence	3 (3.0)	9 (8.7)	8 (7.6)
SKIN & APPENDAGES			
Rash	1 (1.0)	3 (2.9)	4 (3.8)
SPECIAL SENSES			
Unpleasant taste	3 (3.0)	17 (16.3)	36 (34.3)

1: And more frequent in at least one active treatment group than the placebo group.
TEAE=treatment emergent adverse event; ESZ=eszopiclone
COSTART Coding, ITT Population

Treatment Emergent Adverse Events in Placebo-Controlled Clinical Trials with Dosing up to 6-months in Non-Elderly Adults

The types of adverse events reported were similar to those observed during the 6-week trial in the same population. Additional adverse events reported more frequently with eszopiclone compared to placebo included nausea (7.4% vs 5.2%) and pharyngitis (8.1% vs 4.4%).

Treatment-Emergent Adverse Events in Patients with Medical Co-morbidities

In 2 clinical studies of 8 weeks duration where eszopiclone was administered in combination with a selective serotonin reuptake inhibitor (SSRI) in non-elderly adults with Major Depressive Disorder or General Anxiety Disorder, incidences of adverse events were usually similar between the placebo and the eszopiclone groups. Adverse events that were reported more frequently in the eszopiclone group compared to the placebo group included asthenia (7.5% vs 5.1%), dry mouth (12.6% vs 9.2%), somnolence (11.5% vs 8.7%), dizziness (7.5% vs 4.0%), pharyngitis (5.9% vs 3.7%) and unpleasant taste (23.4% vs 2.3%) respectively.

In a 4-week study including non-elderly adults with insomnia and rheumatoid arthritis (RA) reported adverse events were generally similar to those reported in the 4-6-week studies in non-elderly adults, with the following exceptions. In this study, asthenia (6.5% and 1.3%),

pharyngitis (5.2% and 0%), and RA (18.2% and 9.2%, captured as adverse events in this trial) were more prevalent among 3 mg eszopiclone-treated subjects compared with placebo-treated subjects, respectively. Treatment with eszopiclone 3 mg did not result in any worsening of the underlying RA in these subjects.

Less Common Clinical Trial Adverse Drug Reactions
Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse reactions are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse reactions are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse reactions are those that occurred in fewer than 1/1,000 patients. Gender-specific reactions are categorized based on their incidence for the appropriate gender.

Body as a Whole: **Frequent:** chest pain; **Infrequent:** allergic reaction, cellulitis, face edema, fever, halitosis, heat stroke, hernia, malaise, neck rigidity, photosensitivity.

Cardiovascular System: **Frequent:** migraine; **Infrequent:** hypertension; **Rare:** thrombophlebitis.

Digestive System: **Infrequent:** anorexia, cholelithiasis, increased appetite, melena, mouth ulceration, thirst, ulcerative stomatitis; **Rare:** colitis, dysphagia, gastritis, hepatitis, hepatomegaly, liver damage, stomach ulcer, stomatitis, tongue edema, rectal hemorrhage.

Hemic and Lymphatic System: **Infrequent:** anemia, lymphadenopathy.

Metabolic and Nutritional: **Frequent:** peripheral edema; **Infrequent:** hypercholesterolemia, weight gain, weight loss; **Rare:** dehydration, gout, hyperlipemia, hypokalemia.

Musculoskeletal System: **Infrequent:** arthritis, bursitis, joint disorder (mainly swelling, stiffness, and pain), leg cramps, myasthenia, twitching; **Rare:** arthrosis, myopathy.

Nervous System: **Infrequent:** agitation, apathy, ataxia, emotional lability, hostility, hypertonia, hypesthesia, incoordination, insomnia, memory impairment, neurosis, nystagmus, paresthesia, reflexes decreased, thinking abnormal (mainly difficulty concentrating), vertigo; **Rare:** abnormal gait, euphoria, hyperesthesia, hypokinesia, neuritis, neuropathy, stupor, tremor.

Respiratory System: **Infrequent:** asthma, bronchitis, dyspnea, epistaxis, hiccup, laryngitis.

Skin and Appendages: **Infrequent:** acne, alopecia, contact dermatitis, dry skin, eczema, skin discoloration, sweating, urticaria; **Rare:** erythema multiforme, furunculosis, herpes zoster, hirsutism, maculopapular rash, vesiculobullous rash.

Special Senses: **Infrequent:** conjunctivitis, dry eyes, ear pain, otitis externa, otitis media, tinnitus, vestibular disorder; **Rare:** hyperacusis, iritis, mydriasis, photophobia, ptosis.

Urogenital System: **Infrequent:** amenorrhea, breast engorgement, breast enlargement, breast

neoplasm, breast pain, cystitis, dysuria, female lactation, hematuria, kidney calculus, kidney pain, mastitis, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, uterine hemorrhage, vaginal hemorrhage, vaginitis; **Rare:** oliguria, pyelonephritis, urethritis.

Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs

Next-Day Residual Effects

In a double-blind study of 91 healthy adults age 25- to 40- years, the effects of LUNESTA 3 mg on psychomotor function were assessed between 7.5 and 11.5 hours the morning after dosing. Measures included tests of psychomotor coordination that are correlated with ability to maintain a motor vehicle in the driving lane, tests of working memory, and subjective perception of sedation and coordination. Compared with placebo, LUNESTA 3 mg was associated with next-morning psychomotor and memory impairment that was most severe at 7.5 hours, but still present and potentially clinically meaningful at 11.5 hours. Subjective perception of sedation and coordination from LUNESTA 3 mg was not consistently different from placebo, even though subjects were objectively impaired.

In a 6-week adult study of nightly administered LUNESTA, confusion was reported by 3% of patients treated with LUNESTA 3 mg compared to 0% of subjects treated with placebo. In the same study, memory impairment was reported by 1% of patients treated with either 2 mg or 3 mg LUNESTA, compared to 0% treated with placebo.

In a 6-month double-blind, placebo-controlled trial of nightly administered LUNESTA 3 mg, memory impairment was reported by 1.3% (8/593) of subjects treated with LUNESTA 3 mg compared to 0% (0/195) of subjects treated with placebo.

In a 2-week study of 264 elderly insomniacs, 1.5% of patients treated with LUNESTA 2 mg reported memory impairment compared to 0% treated with placebo. In another 2-week study of 231 elderly insomniacs, 2.5% of patients treated with LUNESTA 2 mg reported confusion compared to 0% treated with placebo.

Withdrawal Events

In a 6-month double-blind, placebo-controlled study of nightly administration of LUNESTA 3 mg, rates of anxiety reported as an adverse event were 2.1% in the placebo arm and 3.7% in the LUNESTA arm. In a 6-week adult study of nightly administration, anxiety was reported as an adverse event in 0%, 2.9%, and 1.0% of the placebo, 2 mg, and 3 mg treatment arms, respectively. In this study, single-blind placebo was administered on nights 45 and 46, the first and second days of withdrawal from study drug. New adverse events were recorded during the withdrawal period, beginning with day 45, up to 14 days after discontinuation. During this withdrawal period, 105 subjects previously taking nightly LUNESTA 3 mg for 44 nights spontaneously reported anxiety (1%), abnormal dreams (1.9%), hyperesthesia (1%), and neurosis (1%), while none of 99 subjects previously taking placebo reported any of these adverse events during the withdrawal period.

Rebound Insomnia

Rebound insomnia, defined as a dose-dependent temporary worsening in sleep parameters compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. Rebound insomnia with LUNESTA was assessed objectively in a 6-week adult study on the first 2 nights of discontinuation (nights 45 and 46) following 44 nights of active treatment with 2 mg or 3 mg. In the LUNESTA 2 mg group, compared with baseline, there was a significant increase in WASO and a decrease in sleep efficiency, both occurring only on the first night after discontinuation of treatment. No changes from baseline were noted in the LUNESTA 3 mg group on the first night. Comparisons of changes from baseline between LUNESTA and placebo were also performed. On the first night after discontinuation of LUNESTA 2 mg, LPS and WASO were significantly increased and sleep efficiency was reduced; there were no significant differences on the second night. On the first night following discontinuation of LUNESTA 3 mg, sleep efficiency was significantly reduced. No other differences from placebo were noted in any other sleep parameter on either the first or second night following discontinuation. For both doses, the discontinuation-emergent effect was mild, had the characteristics of the return of the symptoms of chronic insomnia, and appeared to resolve by the second night after LUNESTA discontinuation.

Post-Market Adverse Drug Reactions

In addition to the adverse reactions observed during clinical trials, dysosmia, an olfactory dysfunction that is characterized by distortion of the sense of smell, has been reported during post-marketing surveillance with LUNESTA. Because this event is reported spontaneously from a population of unknown size, it is not possible to estimate the frequency of this event.

DRUG INTERACTIONS

Overview

Because eszopiclone is metabolized by CYP3A4 and CYP2E1 via demethylation and oxidation, there is a potential for interaction with other drugs metabolized by these enzymes. The exposure of eszopiclone was increased by co-administration of ketoconazole, a potent inhibitor of CYP3A4 (see also Table 3). Other potent inhibitors of CYP3A4 would be expected to behave similarly.

Concomitant use with alcohol and other CNS-depressants may enhance the sedative effects of eszopiclone.

Drug-Drug Interactions

General

Alcohol

Concomitant intake with alcohol is not recommended (see boxed **SERIOUS WARNINGS AND PRECAUTIONS: COMPLEX SLEEP-RELATED BEHAVIOURS**). LUNESTA may produce additive CNS depressant effects when co-administered with alcohol.

CNS Depressants
LUNESTA may produce additive CNS depressant effects when co-administered with sedative antihistamines, anticonvulsants, narcotic analgesics, anesthetics, or psychotropic medications such as antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, and antidepressant agents which themselves can produce CNS depression. In the case of narcotic analgesics, enhancement of euphoria may also occur, leading to an increase in psychological dependence.

Opioids
Due to additive CNS depressant effect, the concomitant use of benzodiazepines or other CNS depressants, including LUNESTA, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see boxed **SERIOUS WARNINGS AND PRECAUTIONS: RISKS FROM CONCOMITANT USE WITH OPIOIDS**, and **WARNINGS AND PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines or other CNS depressants**).

Table 3. Established or Potential Drug-Drug Interactions

Drug name	Ref	Effect	Clinical comment
Ethanol	CT	An additive effect on psychomotor performance was seen with co-administration of eszopiclone and ethanol 0.70 g/kg for up to 4 hr after ethanol administration.	Caution is warranted when LUNESTA is administered with ethanol. See **DOSAGE AND ADMNISTRATION, Special Populations, Use with CNS Depressants**.
Paroxetine	CT	Co-administration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.	No dosage adjustment is necessary when LUNESTA is administered with paroxetine.
Lorazepam	CT	Coadministration of single doses of eszopiclone and lorazepam did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.	No dosage adjustment is necessary when LUNESTA is administered with lorazepam. See **also DOSAGE AND ADMINISTRATION, Special Populations, Use with CNS Depressants.**
Olanzapine	CT	Co-administration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there were no alterations in the pharmacokinetics of either drug.	A reduction in dose is necessary when eszopiclone is administered with agents having known CNS-depressant effects.

Ketoconazole	CT	The AUC of eszopiclone was increased 2.2-fold by co-administration with ketoconazole 400 mg daily for 5 days. C_{max} and $t_{½}$ was increased 1.4-fold and 1.3-fold, respectively. See **DETAILED PHARMACOLOGY, Human Pharmacology, Pharmacokinetics.**	A reduction in dose may be warranted in patients taking LUNESTA with ketoconazole and other potent CYP3A4 inhibitors. The dose should not exceed 2 mg.
Rifampin	CT	Racemic zopiclone exposure was decreased by 80% by concomitant use of rifampin.	A similar effect would be expected with eszopiclone.
Digoxin	CT	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.	No dosage adjustment is necessary when LUNESTA is administered with digoxin.
Warfarin	CT	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 following a single 25 mg oral dose of warfarin.	No dosage adjustment is warranted when LUNESTA is administered with warfarin.

Legend: CT = Clinical Trial

In patients with mood disorders, co-administration of eszopiclone with fluoxetine or escitalopram did not adversely affect the pharmacodynamic effects of eszopiclone or the antidepressant agents.

Drug-Food Interactions
Co-administration of LUNESTA with or immediately after a high-fat meal results in slower absorption. Therefore, the effects of LUNESTA on sleep onset may be slightly reduced if it is taken with or immediately after a high-fat or heavy meal (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The length of treatment should be for the minimum duration necessary for the patient. Treatment with LUNESTA should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.
- Taking LUNESTA with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of LUNESTA on sleep latency (see **ACTION AND CLINICAL PHARMACOLOGY**).
- LUNESTA tablets must not be broken or crushed prior to ingestion.

Recommended Dose and Dosage Adjustment

Adult

The recommended starting dose is 1 mg. The dose can be increased to 2 mg or 3 mg if clinically indicated. Use the lowest effective dose of LUNESTA possible for the patient. In some patients, the higher morning blood levels of LUNESTA following use of the 2 mg or 3 mg dose, increase the risk of next day impairment of driving and other activities that require full alertness. The total dose of LUNESTA should not exceed 3 mg, once daily immediately before bedtime (see **WARNINGS AND PRECAUTIONS, CNS Depressant Effects and Next-Day Impairment**).

Special Populations

Geriatrics (> 65 years of age)

In elderly or debilitated patients, the total dose of LUNESTA should not exceed 2 mg.

Pediatrics (< 18 years of age)

LUNESTA is not indicated for patients under 18 years of age.

Hepatic Impairment, Renal Impairment or Use with Potent CYP 3A4 Inhibitors

In patients with severe hepatic or renal impairment or in patients coadministered LUNESTA with potent CYP3A4 inhibitors, the total dose of LUNESTA should not exceed 2 mg.

Use with CNS Depressants

Dosage adjustments may be necessary when LUNESTA is combined with other CNS depressant drugs because of the potentially additive effects.

Missed Dose

If a dose is missed, do not take in the middle of the night. Patients should wait and take the next dose at bedtime the next night, if a dose is needed.

Administration

LUNESTA should be taken orally immediately before retiring or when in bed.

OVERDOSAGE

In clinical studies with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Since commercial marketing began, spontaneous cases of overdose up to 270 mg (90 times the maximum recommended dose of eszopiclone) have been reported, in which patients have recovered. Fatal overdose is more likely to occur when eszopiclone is taken in combination with other CNS depressants including alcohol.

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. Methemoglobinemia in association with overdose of racemic zopiclone has been reported. 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; however, flumazenil administration may contribute to the appearance of neurological symptoms (agitation, anxiety, convulsions and emotional lability).

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. Consider monitoring methemoglobin in the setting of high dose overdosage. The value of dialysis in the treatment of overdosage has not been determined.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Eszopiclone is a non-benzodiazepine hypnotic agent, which is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines or barbiturates. The effects of eszopiclone are due to modulation of gamma-aminobutyric acid (GABA)-A-receptor macromolecular complexes, containing alpha-1, alpha-2, alpha-3 and alpha-5 sub-units. GABA-evoked chloride conductance is increased resulting in neuronal hyperpolarisation and thereby inhibiting neuronal transmission and causing sleep. As compared to racemic zopiclone whose effects are mediated predominantly through α1, the effects of eszopiclone are mediated predominantly through the alpha-2 and alpha-3 $GABA_A$.

Pharmacodynamics

Transient Insomnia

In a single night model of transient insomnia in healthy adult volunteers, a 3 mg dose of LUNESTA was superior to placebo on measures of sleep onset and sleep maintenance using objective polysomnography. In addition, self-reported scores for sleep quality and sleep depth were significantly better for LUNESTA compared to placebo and there were statistically significant treatment differences for several sleep architecture parameters.

Pharmacokinetics

Table 4. Steady-State Pharmacokinetic Parameters of Eszopiclone in Healthy Volunteers

	C_{max} (ng/ml)	**$t_{½}$ (h)**	**AUC_{0-4}**	**T_{max} (h)**
Eszopiclone				
3 mg	26.18 ± 6.56	7.03 ± 4.00	191.07 ± 60.88	1.13 ± 0.48

Absorption: Eszopiclone is rapidly absorbed, with a time to peak concentration (t_{max}) of approximately 1 hour and a terminal-phase elimination half-life ($t_{½}$) of approximately 7 hours.

In healthy adults, LUNESTA does not accumulate with once-daily administration, and its exposure is dose-proportional over the range of 1 to 6 mg.

In healthy adults, administration of eszopiclone after a high fat meal resulted in no change in AUC, a reduction in mean C_{max} of 21%, and delayed t_{max} by approximately 1 hour. The half-life remained unchanged. The effects of LUNESTA on sleep onset may be slightly reduced if it is taken with or immediately after a high-fat or heavy meal.

Distribution: Eszopiclone is weakly bound to plasma protein (52-59%). Therefore, eszopiclone disposition is unlikely to be affected by drug-drug interactions caused by protein binding. The blood-to-plasma ratio for eszopiclone is less than one, indicating no selective uptake by red blood cells.

Metabolism: Following oral administration, eszopiclone is extensively metabolized by oxidation and demethylation. The primary plasma metabolites are (S)-zopiclone-N-oxide and (S)-N-desmethyl zopiclone; the latter compound binds to GABA receptors with substantially lower potency than eszopiclone, and the former compound shows no significant binding to this receptor. *In vitro* studies have shown that CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes. In humans, co-administration with ketoconazole resulted in increased exposure to eszopiclone. Potent inducers of CYP3A4 would be expected to reduce systemic exposure to eszopiclone.

Excretion: After oral administration, eszopiclone is eliminated with a mean $t_{½}$ of approximately 7 hours. Up to 75% of an oral dose of racemic zopiclone is excreted in the urine, primarily as metabolites. A similar excretion profile would be expected for eszopiclone, the S-isomer of

racemic zopiclone. Less than 10% of the orally administered eszopiclone dose is excreted in the urine as parent drug.

Special Populations and Conditions

Geriatrics: Compared with non-elderly adults, subjects 65 years and older had an increase of 41% in exposure (AUC) and prolonged elimination of eszopiclone ($t_{½}$ approximately 9 hours). C_{max} was unchanged. Therefore, in elderly patients the dose of LUNESTA must not exceed 2 mg.

Hepatic Insufficiency: Pharmacokinetics of a 2 mg dose were assessed in 8 subjects with mild, moderate, and severe liver disease and compared to 16 healthy volunteers. Exposure was increased 2-fold and elimination of eszopiclone prolonged ($t_{½}$ approximately 15 hrs) in severely impaired patients compared with healthy volunteers. C_{max} and t_{max} were unchanged. No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment. In non-elderly adults with severe hepatic impairment, the recommended dose is 2 mg. LUNESTA is contraindicated in elderly patients with severe hepatic impairment.

Renal Insufficiency: The pharmacokinetics of eszopiclone were studied in 24 subjects with mild, moderate or severe renal impairment. Compared with healthy subjects, subjects with severe renal impairment had an increase in exposure (AUC) of 47%. The dose of LUNESTA in patients with severe renal impairment should not exceed 2 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment.

STORAGE AND STABILITY

Store at 15 to 30^{o}C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LUNESTA (eszopiclone) is a round, tablet containing 1 mg, 2 mg, or 3 mg of eszopiclone. Tablets are film coated and debossed on one side. LUNESTA 1 mg tablets are light blue and debossed with “L 34” on one side. LUNESTA 2 mg tablets are white and debossed with “L 35” on one side. LUNESTA 3 mg tablets are dark blue and debossed with “L 36” on one side. The 1 mg tablets are supplied in bottles of 30 tablets. The 2 and 3 mg tablets are supplied in bottles of 100 tablets. The 1 mg and 3 mg tablets are supplied in PVC/PE/PVdC-aluminium foil blisters, with 3 tablets per blister strip in a carton.

LUNESTA contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate dihydrate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose,. Film coating ingredients include: Opadry® blue: FD&C Blue #2, hypromellose, macrogol, titanium dioxide and triacetin (1 mg only), Opadry® white: hypromellose, macrogol, titanium dioxide and triacetin (2 mg only), Opadry® blue: FD&C Blue #2, hypromellose, macrogol, titanium dioxide and triacetin (3 mg only).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

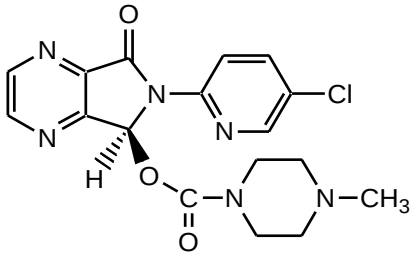
Drug Substance

Proper name: Eszopiclone

Chemical name: (+)-(5S)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazin-5-yl 4-methylpiperazine-1-carboxylate

Molecular formula and molecular mass: $C_{17}H_{17}ClN_6O_3$
388.81

Structural formula:



Physicochemical properties: Eszopiclone is a white to light-yellow crystalline solid.

Eszopiclone is very slightly soluble in water, slightly soluble in ethanol and soluble in phosphate buffer (pH 3.2).

Eszopiclone has a single chiral centre with an (*S*)-configuration.

CLINICAL TRIALS

Trial Design

The effect of LUNESTA on sleep latency and sleep maintenance was studied in four clinical trials involving 1441 patients of which 827 received eszopiclone 1, 2, or 3 mg. Two of these trials were in elderly patients (n=523), one was a 6-week trial in non-elderly adults (n=308), and one was a 6-month trial (n=828).

All studies were randomized, double-blind, and placebo-controlled.

The primary efficacy measures of the studies were:

- objective (polysomnographic) latency to persistent sleep (LPS) in 3 studies;
- objective LPS and objective sleep efficiency (as co-primary endpoints) in one study;
- subjective sleep latency (measured with an interactive phone system) in 2 studies.

Secondary measures of efficacy included quality of sleep, sleep architecture, Insomnia Severity Index (ISI) total scores, Epworth Sleep Scale (ESS) scores, and quality of life measures.

Study Results

Overall, at the usual effective adult dose (2-3 mg) and elderly dose (1-2 mg), LUNESTA significantly decreased sleep latency and improved measures of sleep maintenance [objectively measured as wake time after sleep onset (WASO) and subjectively measured as total sleep time (TST)]. In non-elderly adults, a 1 mg dose demonstrated inconsistent efficacy in improving sleep onset or wakefulness and did not improve total sleep time in any study.

Adults

In the first study, adults with insomnia (n=308) were evaluated in a double-blind, parallel-group trial of 6 weeks' duration comparing LUNESTA 2 mg and 3 mg with placebo. Objective (polysomnographic) endpoints were measured for 4 weeks. For the primary endpoint, LPS, both 2 mg and 3 mg were superior to placebo at 4 weeks. The 3 mg dose was superior to placebo on WASO.

In a long term 6 month, double-blind, placebo controlled study, eszopiclone 3 mg was superior to placebo in reduction in subjective sleep latency for the month 4-6 average (pairwise test, $p<0.0001$). Subjective sleep latency for the month 1-3 average, total sleep time and WASO were also improved when eszopiclone 3 mg was compared to placebo.

Elderly

Elderly subjects (ages 65-86) with insomnia were evaluated in two double-blind, parallel-group trials of 2 weeks duration. One study (n=231) compared the effects of 1 and 2 mg of LUNESTA with placebo on subjective outcome measures, and the other (n=292) compared the effects of 2 mg with placebo on objective and subjective outcome measures. All doses were superior to placebo on measures of sleep latency. In both studies, sleep maintenance was improved with 2 mg of LUNESTA compared to placebo.

DETAILED PHARMACOLOGY

Human Pharmacology

Pharmacokinetics

Absorption and Bioavailability

Eszopiclone was rapidly absorbed following oral administration, with t_{max} occurring at 1 hour post-dose in healthy subjects.

The plasma concentration profile of eszopiclone was characterized by a bi-exponential decline with an apparent terminal phase $t_{½}$ of approximately 7 hours. Eszopiclone exhibited dose-proportional pharmacokinetics over the range of 1 to 6 mg once daily. No accumulation of eszopiclone was observed following 7 days of once daily drug administration.

The steady-state pharmacokinetic profile of eszopiclone following multiple daily administration of 3 mg eszopiclone in healthy elderly subjects demonstrated an increased AUC and exposure in the elderly by 41% and 56%, respectively, compared to non-elderly subjects. The $t_{½}$ was approximately 2.5 hours longer in the elderly. A decrease in eszopiclone dose to 2 mg is recommended in the elderly.

The effect of a high fat meal on the pharmacokinetics of single doses of eszopiclone was examined and no effect on the AUC was found. There was a decrease in peak plasma concentration of eszopiclone with food (21-39% decrease in C_{max}). The rate of absorption of eszopiclone (t_{max}) was prolonged by 1.0 – 1.5 hours in the presence of food.

The pharmacokinetics of a 2 mg dose were assessed in subjects with mild, moderate, and severe liver disease and compared to healthy volunteers. Eszopiclone C_{max} decreased by 13%, 29%, and 25% in subjects with mild, moderate, and severe hepatic impairment, respectively. $AUC_{(0\text{-last})}$ was unchanged in subjects with mild or moderate hepatic impairment; however, systemic exposure was increased by 74% in subjects with severe hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. The dose should not exceed 2 mg in non-elderly patients with severe hepatic impairment.

During multiple daily dose co-administration of 3 mg eszopiclone and 400 mg ketoconazole, eszopiclone $AUC_{(0\text{-}\tau)}$ was increased by 125%, C_{max} by 43% and $t_{½}$ by 2.2 hours. The rate of absorption was unchanged, suggesting that the increased exposure resulted from CYP3A4 inhibition rather than from an interaction at the absorption level. A decrease in eszopiclone dose to 2 mg is recommended upon co-administration with ketoconazole or compounds which similarly inhibit CYP3A4.

Distribution and Protein Binding

In vitro protein binding of eszopiclone in human plasma was 52-59% over the concentration range of 5-500 ng/mL of [^{14}C]-eszopiclone. Non-specific binding of eszopiclone was less than 5% at concentrations of 1000 ng/mL or below. The relatively low plasma protein binding suggest that reduction in albumin concentration typically observed in severe renal and liver diseases would be expected to result in a negligible change in unbound eszopiclone concentration.

Racemic zopiclone was widely distributed with an absolute volume of distribution of approximately 90 L. Eszopiclone would be expected to exhibit similar distributive properties. A relatively high free fraction (eszopiclone was 52-59% bound to plasma proteins in healthy subjects) was also consistent with a large volume of distribution.

Metabolism and Excretion

The ability of different CYP450 isoforms to metabolize eszopiclone was determined by incubating eszopiclone and human liver microsomes in the presence or absence of selective CYP450 isoform inhibitors. The rate of disappearance of eszopiclone, 10, 100 and 200 µM, was decreased by 63% to 74% in human liver microsomes preincubated with the CYP2E1 inhibitor 4-methylpyrazole. In the presence of ketoconazole, a standard inhibitor of CYP3A4, the rate of disappearance of eszopiclone declined by 44% to 72% as compared to control (over 30 minutes). No significant decline in the disappearance of eszopiclone was seen in human liver microsomes preincubated with other cytochrome isoform inhibitors. This indicated that the metabolism of eszopiclone was catalyzed by CYP3A4 and CYP2E1.

The potential of eszopiclone to inhibit human liver CYP450 isoforms was determined in cryopreserved human hepatocytes in the presence and absence of standard probe substrates. Eszopiclone did not cause inhibition of the metabolism of specific substrates of the CYP450 isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 in human hepatocytes at concentrations up to 100 µM. This demonstrated that eszopiclone was not a CYP450 inhibitor.

In vivo studies indicated that eszopiclone is metabolized by CYP3A4 and CYP2E1 into two primary metabolites, (S)-desmethylzopiclone and zopiclone N-oxide. These metabolites did not possess significant sleep-inducing activity in preclinical models.

Pharmacokinetic studies demonstrated that renal excretion is the principal route of elimination of eszopiclone and its metabolites. Up to 75% of an oral dose of racemic zopiclone is excreted in the urine primarily as metabolites. A similar excretion profile would be expected for eszopiclone. Less than 10% of the dose was excreted in the urine as unchanged drug. The formation and disposition of the primary metabolites were consistent with a linear pharmacokinetic system.

TOXICOLOGY

Single-Dose Toxicity Studies

Acute toxicity testing demonstrated that eszopiclone possesses a low order of acute toxicity. Signs of toxicity included those effects expected for hypnotic agents and were comparable across test articles at the toxic doses evaluated. The safety margin for an acute oral dose is high relative to the maximum clinical daily dose of eszopiclone.

Results from acute toxicity studies are presented in Table 5.

Table 5. Results of Single-Dose Toxicity Studies

Species/ Strains	Route	Dose Levels (mg/kg)	Max. Non-Lethal Dose (mg/kg)	Noteworthy Findings
Mouse/ CD-1	Oral gavage	900, 1200, 1500	<900	- The median lethal dose following oral administration in mice exceeds 900 mg/kg for eszopiclone - All deaths occurred within 4 days following oral administration
Rats/ Sprague-Dawley	IV	1, 10, 25, 75, 100, 250	1 M 75 F	- In rats, the median lethal intravenous dose of eszopiclone was between 1 and 10 mg/kg for males and 100-250 mg/kg for females - All deaths occurred within 1 hour for intravenous administration.

Repeat-Dose Toxicity Studies

Subchronic studies in mice demonstrated that eszopiclone was well tolerated at oral doses up to 200 mg/kg/day for 3 months. Subchronic studies in rats demonstrated that eszopiclone was tolerated at doses up to 100 mg/kg/day for 28 days with lethalities observed at doses ≥200 mg/kg/day for 28 days. Subchronic studies in dogs demonstrated that eszopiclone was tolerated at doses of 2 mg/kg/day (males) and 20 mg/kg/day (females) for 28 days and doses of 2.5 mg/kg/day (males) or 10 mg/kg/day (females) for 3 months.

Treatment-related findings were consistent with exaggerations of the known pharmacologic effects of eszopiclone and were demonstrated to be fully reversible.

Table 6. Results of Repeat-Dose Toxicity Studies

Species/ Strains	Study Duration	Dose Range (mg/kg/day)	Noteworthy Findings
Mouse/ CD-1	1 & 3 mths	50 to 400 NOAEL: 200 mg/kg/day	- Exaggeration of pharmacologic effects (prostration, unsteady gait, labored breathing, hunched posture, etc.), decreased food consumption and body weight. - At higher doses (≥300 mg/kg/day) signs of intolerance included body weight loss and lethality
Rats/ Sprague-Dawley	1, 3 & 18[a] mths	20 to 300 NOAEL: M <25 mg/kg/day F 100 mg/kg/day	- Exaggeration of pharmacologic effects demonstrated to be fully reversible: decreased body weight. - Reproductive system: ≥50 mg/kg/day: decreased testes weight with epididymide effects including edema, epithelium vacuolation and cellular luminal debris, decreased sperm concentration and motility and were fully reversible. Clinical trials have confirmed that these effects are not relevant in humans.
Dogs/ Beagle	1, 3 & 12[a] mths	2 to 25 NOAEL: M 2.5 mg/kg/day F 10 mg/kg/day	- Exaggeration of pharmacologic effects demonstrated to be fully reversible, decreased body weight - At higher doses (≥10 mg/kg/day for 3 months), signs of intolerance included marked CNS effects and lethalities. - Reproductive system: histopathologic changes noted in epididymis (slight spermatocele & focal interstitial granulomatous inflammation, sperm granulomas). Clinical trials have confirmed that these effects are not relevant in humans.

[a] Data from racemic (RS) zopiclone (not shown)

Genotoxicity

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* 32P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Carcinogenicity

In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumours 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 tumours 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 tumours were due to skin lesions induced by aggressive behaviour, 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 tumours 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 tumours in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Juvenile Toxicity

In studies in which eszopiclone (2 to 300 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, neurobehavioural impairment (altered auditory startle response) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were observed at doses ≥ 5 mg/kg/day. Delayed sexual maturation was noted in

males and females at ≥10 mg/kg/day. The no-effect dose (2 mg/kg) was associated with plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures in humans at the maximum recommended dose (MRHD) in adults (3 mg/day).

When eszopiclone (doses from 1 to 50 mg/kg/day) was orally administered to young dogs from weaning through sexual maturity, neurotoxicity (convulsions) was observed at doses ≥ 5 mg/kg/day. Hepatotoxicity (elevated liver enzymes and hepatocellular vacuolation and degeneration) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were noted at dose ≥10 mg/kg/day. The no-effect dose (1 mg/kg) was associated with plasma exposures (AUC) to eszopiclone and (S)-DMZ approximately 3 and 2 times, respectively, plasma exposures in humans at the MRHD in adults.

Reproduction and Development Toxicity

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 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 pre-implantation 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).

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 MHRD 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 post-implantation 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 behavioural measures or reproductive function in the offspring.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrLUNESTA®
eszopiclone tablets

Read this carefully before you start taking **LUNESTA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LUNESTA**.

Serious Warnings and Precautions

Complex sleep-related behaviours
There have been reports of people getting out of bed while not fully awake after taking LUNESTA and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behaviour can occur after taking just a single dose of LUNESTA by itself, but it is more likely to occur when LUNESTA is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

Important:
- Do not take more LUNESTA than prescribed.
- Do not take LUNESTA if you drink alcohol.
- Do not take LUNESTA if you have ever experienced behaviours, as described above, with any other medication, including LUNESTA.
- Talk to your doctor if you have a condition that affects your sleep, such as Periodic Limb Movement in Sleep (involuntary movement of limbs during sleep) or Restless Legs Syndrome (urge to move legs, usually accompanied by uncomfortable and unpleasant sensations, that begins or worsens during periods of inactivity, typically in the evening and night)
- Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take LUNESTA with your other medicines.
- You and people close to you should watch for the type of unusual behaviour described above. If you find out, or suspect that you have done any such activities for which you have no memory, you should stop taking LUNESTA and call your doctor immediately.

Taking opioids
Taking LUNESTA with opioid medicines can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is LUNESTA used for?
LUNESTA is used for a short period of time to help you sleep, including helping you fall asleep,

stay asleep during the night and avoid waking up too early.

Treatment with LUNESTA should usually not go on for more than 7-10 days and should only be used for insomnia where disturbed sleep results in impaired daytime functioning. LUNESTA does not treat the underlying cause of your insomnia.

How does LUNESTA work?
LUNESTA causes a calming effect in your brain and allows you to sleep.

If you are prescribed sleep medications, you should consider both their benefits and risks.

Important risks and limitations include the following:
- You may become dependent on the medication,
- The medication may affect your mental alertness or memory, particularly when not taken as prescribed.

What are the ingredients in LUNESTA?
Medicinal ingredients: Eszopiclone

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate dihydrate, FD&C Blue #2 (1 mg, 3 mg), hypromellose, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, titanium dioxide and triacetin.

LUNESTA comes in the following dosage forms:
Tablets 1 mg, 2 mg, or 3 mg

Do not use LUNESTA if you:
- Have a known allergy to eszopiclone, zopiclone or to any ingredients in the formulation or component of the container
- Have myasthenia gravis, a condition where the muscles easily tire and become weak
- Have severe breathing problems and/or sleep apnea where you stop breathing for short periods while you sleep
- Are elderly and taking certain antifungals or antibiotics (i.e. ketoconazole) or you have severe liver problems
- Have ever experienced a complex sleep-related behaviour (such as driving a car, making and eating food, talking on the phone or having sex while not fully awake) after taking LUNESTA or any other medication.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LUNESTA. Talk about any health conditions or problems you may have, including if you:
- Have a history of depression, mental illness and/or suicidal thoughts or attempts
- Have a history of drug or alcohol abuse or addiction
- Have had unexpected reactions to alcohol or sedative medications in the past, such as irritability, aggression, hallucinations, etc.
- Have liver or kidney problems

- Have a lung disease or breathing problems.
- Have had episodes of sleepwalking in the past, or if there is a history of sleepwalking in your family.
- Have a condition that affects your sleep, such as Periodic Limb Movement Disorder (cramping or jerking of the legs during sleep) or Restless Legs Syndrome (urge to move legs, usually accompanied by uncomfortable and unpleasant sensations that begins or worsens during periods of inactivity, typically in the evening and night).
- You consume alcohol.
- You are taking opioid medicines or other central nervous system depressants such as sedative or hypnotics (see INTERACTIONS WITH THIS MEDICATION), as well as if you are taking any other medicines, including over-the counter medicines and herbal products.
- Are pregnant, planning to become pregnant or breastfeeding
- Are less than 18 years of age

Other warnings you should know about:

- **Complex Sleep-Related Behaviours:** There have been reports of people getting out of bed while not fully awake after taking LUNESTA and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behaviour is more likely to occur when LUNESTA is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc. You and people close to you should watch for this type of unusual behaviour. **Stop taking LUNESTA immediately and call your healthcare professional right away if you find out that you have done any of the above activities after taking LUNESTA.**
- **Mental Alertness:** LUNESTA may affect your ability to be alert next day. DO NOT DRIVE A CAR or operate potentially dangerous machinery:
    - If you do not feel fully awake.
    - If it has not been at least 12 hours since taking the medicine, even if you feel fully awake, especially in elderly patients and in patients who take the 3 mg dose.
    - In all cases, until you experience how the drug affects you next day.
- **Memory Problems:** LUNESTA may cause a special type of memory loss (amnesia); you may not recall events that occurred during some period of time, usually several hours, after taking the drug. This lapse is usually not a problem, because the person taking the sleeping pill intends to be asleep during this critical period of time. But it can be a problem if you take the medication to induce sleep while travelling, such as during an airplane flight, because you may wake up before the effect of the drug is gone. This has been called "traveller's amnesia". DO NOT TAKE LUNESTA when a full night's sleep is not possible before you would again need to be active and functional; e.g., an overnight flight of less than 8 hours. Memory lapses may occur in such situations. Your body needs time to eliminate the medication from your system.
- **Dependence and Abuse:** All prescription sleeping pills can cause dependence (addiction), especially when they are used regularly for more than a few weeks or at higher doses. Some people develop a need to continue taking these drugs, not only for continued effects on sleep, but also to avoid withdrawal symptoms. Patients who depend, or have depended at any time

in the past, on alcohol or other drugs may be at particular risk of becoming dependent on drugs like LUNESTA. But **all people are at some risk**. Consider this matter before you take LUNESTA for more than a few weeks.

- **Withdrawal:** Although uncommon, withdrawal symptoms (including stomach pain, headache, increased appetite and insomnia) have been reported after LUNESTA treatment is stopped. Also, on the first few nights after stopping LUNESTA you may find that your insomnia is worse than before taking the sleeping pills. This type of withdrawal symptom is known as "rebound insomnia".
- **Mental and Behavioural Changes:** A variety of abnormal thinking and behavioural changes may occur when you use prescription sleeping pills. Some of these changes include aggressiveness and extroversion which seem out of character. Other changes, although rare, can be more unusual and extreme. These include confusion, strange behaviour, restlessness, agitation, irritability, nightmares, hallucinations, delusion (a false belief or wrong judgment, held with conviction despite evidence to the contrary), feeling like you are not yourself, and feeling more depressed, which may lead to suicidal thinking. It is rarely clear whether such symptoms are caused by the medication, or by an illness that was present before the medication was used, or are simply spontaneous happenings. If you develop any unusual, disturbing thoughts or behaviour while using LUNESTA, discuss the matter immediately with your healthcare professional.
- **Worsening of Side Effects:** DO NOT CONSUME ALCOHOL WHILE TAKING LUNESTA. Some medicines may also worsen the side effects that some patients experience with LUNESTA.
- **Risk of Falls:** LUNESTA can cause drowsiness, dizziness, lightheadedness and a decreased level of wakefulness, which could increase your risk of falling. Elderly patients in particular are at an increased risk of falls and fractures. Always take LUNESTA right before bed or once already in bed.
- **Effects on Pregnancy:** Certain sleeping pills have been linked to birth defects when taken during the early months of pregnancy. It is not yet known if LUNESTA could cause similar effects. In addition, sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. Therefore, DO NOT TAKE LUNESTA at anytime during pregnancy, it may affect the developing baby.
- **Use in Nursing Mothers:** LUNESTA passes into breast milk. Therefore, if you are breast feeding, this medicine should be avoided. Your healthcare professional will discuss this with you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LUNESTA:

- Alcohol
- Other sedative drugs or sleeping pills
- Narcotic analgesics (opioids) (see Serious Warnings and Precautions box)
- Olanzapine used to treat schizophrenia and bipolar disorder
- Ketoconazole an antifungal used to treat fungal infections
- Rifampin an antibiotic used to treat infections

How to take LUNESTA:

- Do not take more than one dose in a single night.
- Do not take LUNESTA unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.
- Take LUNESTA right before you get into bed, not sooner.
- LUNESTA may take longer to work if you take it with or immediately after eating a large meal.
- Do not break or crush the LUNESTA tablets.
- Do not take a higher dose of LUNESTA than was prescribed by your healthcare professional.
- Do not take LUNESTA if it is not prescribed for you.
- Treatment with LUNESTA should usually not be longer than 7-10 consecutive days. Do not take LUNESTA for more than 7-10 days without first consulting your healthcare professional. If you still have problems sleeping after you finish your tablets, contact your healthcare professional again.
- Do not take LUNESTA if you drink alcohol.
- LUNESTA is not indicated for patients under 18 years of age. Do not take LUNESTA if you are under 18 years of age.

Usual adult dose:

The recommended starting dose for LUNESTA is 1 mg immediately before bedtime. Depending on how you respond to LUNESTA, your healthcare professional may increase the dose to 2 mg or 3 mg. The maximum daily dose in adults is 3 mg.

The maximum dose in the elderly and patients who are weak or sick is 2 mg immediately before bedtime.

The maximum dose is 2 mg for patients also taking certain antifungals or antibiotics (i.e., ketoconazole) or who have severe kidney or liver problems.

Overdose:

If you think you have taken too much LUNESTA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, do not take it in the middle of the night. You should wait and take the next dose at bedtime the next night, if a dose is needed.

What are possible side effects from using LUNESTA?

These are not all the possible side effects you may feel when taking LUNESTA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Unpleasant taste, dry mouth
- Nausea, stomach upset

- Back pain
- Headache
- Drowsiness
- Dizziness, lightheadedness
- Nervousness
- Abnormal dreams

Elderly patients are especially susceptible to side effects. Excessive drowsiness in the elderly may result in falls and fractures.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Getting out of bed and performing activities while not fully awake (i.e: sleep-driving, sleep-walking, making/eating food, talking on phone)		√	
Abnormal thoughts or behaviours (i.e: aggressiveness, confusion, agitation, hallucinations)	√		
Memory loss		√	
UNCOMMON **Allergic reaction:** swelling of the tongue or throat, trouble breathing, nausea and vomiting			√
Withdrawal effects: abdominal and muscle cramps, vomiting, sweating, tremor, and, very rare cases of convulsions			√
Depressed Mood: sadness, lack of interest in daily activities		√	
Thoughts of death, suicide or self-harm			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 to 30°C).

Keep out of reach and sight of children.

If you want more information about LUNESTA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.sunovion.ca, or by calling 1-866-260-6291.

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