HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zolpimist (zolpidem tartrate) Oral Spray safely and effectively. See full prescribing information for Zolpimist (zolpidem tartrate) Oral Spray.
Zolpimist (zolpidem tartrate) Oral Spray (C-IV)
Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Dosage and Administration (2)	5/2013
Dosage and Administration, Dosage in Adults (2.1)	5/2013
Warnings and Precautions (5)	5/2013

INDICATIONS AND USAGE

Zolpimist (zolpidem tartrate) Oral Spray, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

DOSAGE AND ADMINISTRATION

- Use the lowest dose effective for the patient. (2.1)
- Recommended initial dose is 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. (2.1)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 5 mg for men and women. (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with Zolpimist (zolpidem tartrate) Oral Spray. (2.3)
- The effect of Zolpimist (zolpidem tartrate) Oral Spray may be slowed if taken with or immediately after a meal. (2.4)

DOSAGE FORMS AND STRENGTHS

Each metered actuation (one spray) of Zolpimist (zolpidem tartrate) Oral Spray delivers 5 mg of zolpidem tartrate in 100 µL. After an initial priming of 5 actuations, there are 30 or 60 metered actuations in each child-resistant container. The total number of available doses is dependent on the number of actuations per dose (1 or 2 actuations) and the frequency of priming. (3)

CONTRAINDICATIONS

Known hypersensitivity to zolpidem. (4)

WARNINGS AND PRECAUTIONS

- CNS depressant effects: Impairs alertness and motor coordination. Instruct patients on correct use. (5.1)
- Need to evaluate for co-morbid diagnosis: Reevaluate if insomnia persists after 7 to 10 days of use. (5.2)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)
- "Sleep-driving" and other complex behaviors while fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of sprays feasible to avoid intentional overdose. (5.5)
- Respiratory depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.7, 9.3)

ADVERSE REACTIONS

Most commonly observed adverse reactions were:
Short-term (<10 nights): Drowsiness, dizziness, and diarrhea
Long-term (28-35 nights): Dizziness and drugged feelings (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aytu BioScience, Inc. at 1-855-298-8246, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects. (5.1, 7.1)
- Imipramine: Decreased alertness observed. (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed. (7.1)
- Rifampin: Combination use may decrease effects. (7.2)
- Ketoconazole: Combination use may increase effect. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm. (8.1)
- Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder. (5.4, 8.4)

See 16 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 2/2/2016

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zolpimist (zolpidem tartrate) Oral Spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies *[see Clinical Studies (14)]*. The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness *[see Warnings and Precautions (5.1)]*. The total dose of Zolpimist (zolpidem tartrate) Oral Spray should not exceed 10 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of Zolpimist (zolpidem tartrate) Oral Spray in both of these patient populations is 5 mg once daily immediately before bedtime *[see Warnings and Precautions (5.1); Use in Specific Populations (8.5)]*.

2.3 Use with CNS Depressants

Dosage adjustment may be necessary when Zolpimist (zolpidem tartrate) Oral Spray is combined with other CNS-depressant drugs because of the potentially additive effects *[see Warnings and Precautions (5.1)]*.

2.4 Administration

Zolpimist (zolpidem tartrate) Oral Spray is packaged in a child-resistant container. For detailed instructions on how to use Zolpimist (zolpidem tartrate) Oral Spray, refer to the Patient Instructions for Use (following the Medication Guide). Zolpimist (zolpidem tartrate) Oral Spray must be primed before it is used for the first time. To prime, patients should be told to point the black spray opening away from their face and other people and spray 5 times. For administration, the child-resistant container should be held upright with the black spray opening pointed directly into the mouth. The patient should fully press down on the pump to make sure a full dose (5 mg) of Zolpimist (zolpidem tartrate) Oral Spray is sprayed directly into the mouth over the tongue. If a 10 mg dose is prescribed, a second spray should be administered.

If the patient does not use Zolpimist (zolpidem tartrate) Oral Spray for at least 14 days, it must be primed again with 1 spray. The patient should be referred to the Patient Instructions for Use included at the end of the Medication Guide.

The effect of Zolpimist (zolpidem tartrate) Oral Spray may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Zolpimist (zolpidem tartrate) Oral Spray is available as a clear, colorless, and cherry flavored solution designed to be sprayed directly into the mouth over the tongue. Each metered actuation (one spray) of Zolpimist (zolpidem tartrate) Oral Spray delivers 5 mg of zolpidem tartrate in 100 µL. Two actuations deliver 10 mg of zolpidem tartrate. After an initial priming of 5 actuations, there are 30 or 60 metered actuations in each child-resistant container. The total number of available doses is dependent on one of two available package sizes (i.e., the fill amount in the bottle, either 4.5 mL or 7.7 mL), the number of actuations per dose (1 or 2 actuations), and the frequency of priming.

4 CONTRAINDICATIONS

Zolpimist (zolpidem tartrate) Oral Spray is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions with zolpidem include anaphylaxis and angioedema *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-day Impairment

Zolpimist (zolpidem tartrate) Oral Spray, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustments of Zolpimist (zolpidem tartrate) Oral Spray and of other concomitant CNS depressants may be necessary when Zolpimist (zolpidem tartrate) Oral Spray is administered with such agents because of the potentially additive effects.

The use of Zolpimist (zolpidem tartrate) Oral Spray with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended *[see Dosage and Administration (2.3)]*.

The risk of next-day psychomotor impairment, including impaired driving, is increased if Zolpimist (zolpidem tartrate) Oral Spray is taken with less than a full night of sleep remaining (7 to 8 hours); if a higher than the recommended dose is taken; if co-administered with other CNS depressants; or if co-administered with other drugs that increase the blood levels of zolpidem. Patients should be cautioned against driving and other activities requiring complete mental alertness if Zolpimist (zolpidem tartrate) Oral Spray is taken in these circumstances *[see Dosage and Administration (2) and Clinical Studies (14.3)]*.

5.2 Need to Evaluate for Co-morbid Diagnoses

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 behavioral abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative-hypnotic drugs, including zolpidem.

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. 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 throat, glottis, or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.4 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavioral changes have been reported in patients treated with sedative-hypnotics, including zolpidem tartrate. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation, and depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials of zolpidem tartrate 10 mg taken at bedtime, <1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with zolpidem tartrate 0.25 mg/kg taken at bedtime reported hallucinations, versus 0% treated with placebo *[see Use in Specific Populations (8.4)]*.

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” have occurred with zolpidem tartrate alone at therapeutic doses, the co-administration of zolpidem tartrate with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of zolpidem tartrate at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Zolpimist (zolpidem tartrate) Oral Spray should be strongly considered for patients who report a “sleep-driving” episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving,” patients usually do not remember these events. Amnesia, anxiety, and other neuropsychiatric symptoms may also occur.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is 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.

5.5 Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage 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.

5.6 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Zolpimist (zolpidem tartrate) Oral Spray is prescribed to patients with compromised respiratory function. Postmarketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risks of respiratory depression should be considered prior to prescribing Zolpimist (zolpidem tartrate) Oral Spray in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.7 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence *[see Abuse (9.2) and Dependence (9.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- CNS-depressant effects and next-day impairment *[see Warnings and Precautions (5.1)]*.
- Serious anaphylactic and anaphylactoid reactions *[see Warnings and Precautions (5.3)]*.
- Abnormal thinking and behavior changes, and complex behaviors *[see Warnings and Precautions (5.4)]*.
- Withdrawal effects *[see Warnings and Precautions (5.7)]*.

6.1 Clinical Trials Experience

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem tartrate at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Most commonly observed adverse reactions in controlled trials: During short-term treatment (up to 10 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Adverse reactions observed at an incidence of ≥1% in controlled trials: The following tables enumerate treatment-emergent adverse reaction frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate and at a greater incidence than placebo in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied. The following table was derived from results of 11 placebo-controlled, short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights
(Percentage of patients reporting)

Body System/Adverse Reaction*	**Zolpidem (≤10mg) (n=685)**	**Placebo (n=473)**
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	-

*Reactions reported by at least 1% of patients treated with zolpidem tartrate and at a greater frequency than placebo.

The following table was derived from results of three placebo-controlled, long-term efficacy trials involving zolpidem tartrate. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem tartrate at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse reactions occurring at an incidence of at least 1% for zolpidem tartrate patients.

Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 35 Nights
(Percentage of patients reporting)

Body System/Adverse Reaction*	**Zolpidem (≤10mg) (n=152)**	**Placebo (n=161)**
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-
Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

*Reactions reported by at least 1% of patients treated with zolpidem tartrate and at a greater frequency than placebo.

Dose relationship for adverse reactions*:* There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal adverse reactions.

Oral tissue-related adverse reactions in Zolpimist (zolpidem tartrate) Oral Spray pharmacokinetics studies*:* The effect of chronic daily administrations of Zolpimist (zolpidem tartrate) Oral Spray on oral tissue has not been evaluated. In pharmacokinetic studies conducted with Zolpimist (zolpidem tartrate) Oral Spray in healthy subjects, an oral soft tissue exam was performed and no signs of oral irritation were noted following administration of single doses of Zolpimist (zolpidem tartrate) Oral Spray.

Adverse event incidence across the entire preapproval database*:* Zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the United States, Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified WHO dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem tartrate, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem tartrate. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those

coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with zolpidem tartrate, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic nervous system*:* Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole*:* Frequent: asthenia. Infrequent: edema, falling, fatigue, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system*:* Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system*:* Frequent: ataxia, confusion, euphoria, headache, insomnia, vertigo. Infrequent: agitation, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system*:* Frequent: dyspepsia, hiccup, nausea. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system*:* Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system*:* Infrequent: infection. Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and biliary system*:* Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

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

Musculoskeletal system*:* Frequent: arthralgia, myalgia. Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendonitis.

Reproductive system*:* Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system*:* Frequent: upper respiratory infection, lower respiratory infection. Infrequent: bronchitis, coughing, dyspnea, rhinitis. Rare: bronchospasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages*:* Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

Special senses*:* Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

Urogenital system*:* Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

7 DRUG INTERACTIONS

7.1 CNS-active Drugs

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression *[see Warnings and Precautions (5.1)]*. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

CNS-depressants: Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression *[see Warnings and Precautions (5.1)]*. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated *[see Warnings and Precautions (5.1)]*.

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (-53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem $t_{1/2}$ (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

Drugs that affect drug metabolism via cytochrome P450: Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady state levels in male volunteers resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem tartrate. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (-73%), C_{max} (-58%), and $t_{1/2}$ (-36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination $t_{1/2}$ (30%) along with an increase in the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

Other drugs with no interactions with zolpidem: A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

7.2 Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of drugs on other P450 enzymes on the exposure to zolpidem is not known.

Rifampin: Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of rifampin in combination with zolpidem may decrease the efficacy of zolpidem.

Ketoconazole: Ketoconazole, a potent CYP3A4 inhibitor, increased the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

7.3 Other Drugs with No Interaction with Zolpidem

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in normal subjects.

7.4 Drug-laboratory Test Interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screenings.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Zolpimist (zolpidem tartrate) Oral Spray in pregnant women.

Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy.

Zolpimist (zolpidem tartrate) Oral Spray should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the zolpidem tartrate maximum recommended human dose (MRHD) of 10 mg/day (approximately 8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day, increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m^2 basis.

8.2 Labor and Delivery
Zolpimist (zolpidem tartrate) Oral Spray has no established use in labor and delivery *[see Pregnancy (8.1)]*.

8.3 Nursing Mothers
Zolpidem is excreted in human milk. Caution should be exercised when Zolpimist (zolpidem tartrate) Oral Spray is administered to a nursing woman.

8.4 Pediatric Use
Zolpimist (zolpidem tartrate) Oral Spray is not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

In an 8-week controlled study of pediatric patients (6-17 years of age) with insomnia associated with attention-deficit/hyperactivity-disorder (ADHD), an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations *[see Warnings and Precautions (5.4)]*. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

8.5 Geriatric Use
A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received oral zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem tartrate at doses of ≥10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

Adverse Reaction	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were ≥70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

The dose of Zolpimist (zolpidem tartrate) Oral Spray in elderly patients is 5 mg to minimize the adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative-hypnotic drugs *[see Warnings and Precautions (5.1)]*.

8.6 Gender Difference in Pharmacokinetics
Women clear zolpidem tartrate from the body at a lower rate than men. Maximum concentration (C_{max}) and area under the concentration curve (AUC) parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of Zolpimist (zolpidem tartrate) Oral Spray for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of Zolpimist (zolpidem tartrate) Oral Spray in geriatric patients is 5 mg regardless of gender.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

9.2 Abuse
Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. 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 effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors 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, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

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

9.3 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.

Sedative-hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse reactions which are considered to meet the DSM-III-R criteria for uncomplicated sedative-hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse reactions occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses.

Postmarketing reports of abuse, dependence, and withdrawal have been received.

10 OVERDOSAGE

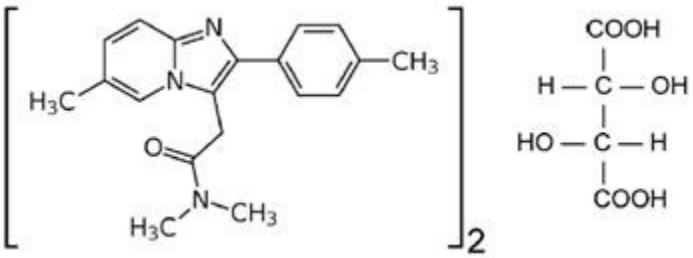
10.1 Signs and Symptoms
In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

10.2 Recommended Treatment
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative-hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). 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.

Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

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.

11 DESCRIPTION
Zolpimist (zolpidem tartrate) Oral Spray is a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class. Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.89.

Zolpimist (zolpidem tartrate) Oral Spray is available as an oral solution designed to be sprayed directly into the mouth over the tongue. Each metered actuation of Zolpimist (zolpidem tartrate) Oral Spray delivers 5 mg of zolpidem tartrate in 100 µL. Two actuations deliver 10 mg of zolpidem tartrate. Zolpimist (zolpidem tartrate) Oral Spray includes the following inactive ingredients: artificial cherry flavor, benzoic acid, citric acid monohydrate, hydrochloric acid, neotame, propylene glycol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the α_1/α_5 subunits.

This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

12.3 Pharmacokinetics

Zolpimist (zolpidem tartrate) Oral Spray is bioequivalent to Ambien® tablets (Sanofi-Aventis).

The pharmacokinetic profile of Zolpimist (zolpidem tartrate) Oral Spray is characterized by rapid absorption from the oral mucosa and gastrointestinal tract, and a short elimination $t_{1/2}$ in healthy subjects.

In a single-dose crossover study in 10 healthy, young (18-40 years of age) male subjects administered 2.5, 5, and 10 mg Zolpimist (zolpidem tartrate) Oral Spray, the results demonstrated a linear relationship to dose for mean C_{max} and $AUC_{0-\infty}$ over the range of doses administered in the study.

In a single-dose crossover study in 43 healthy, young (18-45 years of age) subjects administered 5 and 10 mg Zolpimist (zolpidem tartrate) Oral Spray, the means for C_{max} were 114 (range: 19 to 197) and 210 ng/mL (range: 77 to 401), respectively, occurring at a mean time to maximum concentration (T_{max}) of approximately 0.9 hours for both. The mean zolpidem $t_{1/2}$ was 2.7 (range: 1.7 to 5.0) and 3.0 hours (range: 1.7 to 8.4), for 5 and 10 mg Zolpimist (zolpidem tartrate) Oral Spray, respectively. In the same study, the means for C_{max} were 123 (range: 53 to 221) and 219 ng/mL (range: 101 to 446) for 5 and 10 mg Ambien® tablets, respectively, occurring at a mean T_{max} of 0.9 and 1.0 hours, respectively. The mean zolpidem $t_{1/2}$ was 2.8 (range: 1.5 to 6.0) and 3.1 hours (range: 1.1 to 8.6) for the 5 and 10 mg Ambien® tablets, respectively.

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion. Total protein binding for zolpidem was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate for 2 weeks.

A food-effect crossover study in 14 healthy, young (18-45 years of age) male subjects compared the pharmacokinetics of Zolpimist (zolpidem tartrate) Oral Spray 10 mg when administered while fasting at least 8 hours or 5 minutes after eating a standard high-fat meal. Results demonstrated that with food, mean $AUC_{0-\infty}$ and C_{max} were decreased by 27% and 58%, respectively, while mean C_{max} was prolonged by 225% (from 0.8 to 2.6 hours). These results suggest that, for faster sleep onset, as with all zolpidem products, Zolpimist (zolpidem tartrate) Oral Spray should not be administered with or immediately after a meal.

Special Populations:

Elderly: In the elderly, the dose for zolpidem tartrate should be 5 mg *[see Warnings and Precautions (5) and Dosage and Administration (2)]*. This recommendation is based on several studies in which the mean C_{max}, $t_{1/2}$, and AUC were significantly increased when compared to results in young adults administered zolpidem tartrate. In a pharmacokinetic study of 24 elderly (≥65 years of age) subjects administered 5 mg Zolpimist (zolpidem tartrate) Oral Spray, the means for C_{max} and AUC were 134 ng/mL and 493 ng·hr/mL respectively, following administration of a single 5 mg oral dose of Zolpimist (zolpidem tartrate) Oral Spray. Zolpidem tartrate did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Hepatic impairment: The pharmacokinetics of zolpidem in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean $t_{1/2}$ in cirrhotic patients of 9.9 hours (range: 4.1 to 25.8 hours) was greater than that observed in normal subjects of 2.2 hours (range: 1.6 to 2.4 hours). Dosing should be modified accordingly in patients with hepatic insufficiency *[see Dosage and Administration (2.2)]*.

Renal impairment: The pharmacokinetics of zolpidem were studied in 11 patients with end-stage renal failure (mean Cl_{Cr}=6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, $t_{1/2}$, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg/day. In mice, these doses are approximately 2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m^2 basis. In rats, these doses are approximately 5, 20, and 100 times the MRHD on a mg/m^2 basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Mutagenesis: Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

Impairment of fertility: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 24 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

14 CLINICAL STUDIES

14.1 Transient Insomnia

Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n=35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15, and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

14.2 Chronic Insomnia

Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week.

Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with zolpidem.

14.3 Studies Pertinent to Safety Concerns for Sedative-hypnotic Drugs

Next-day residual effects: Next-day residual effects of zolpidem tartrate were evaluated in seven studies involving normal subjects. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of zolpidem tartrate in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of zolpidem tartrate. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory impairment: Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of zolpidem tartrate. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose) (i.e., these subjects experienced anterograde amnesia). There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of zolpidem tartrate, predominantly at doses above 10 mg.

Effects on sleep stages: In studies that measured the percentage of sleep time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

15 HOW SUPPLIED/STORAGE AND HANDLING

Zolpimist (zolpidem tartrate) Oral Spray is available in a child-resistant container, which secures a bottle filled with either 4.5 mL (4.8 g) or 7.7 mL (8.2 g). Each container includes a child-resistant cap and base with a metered-dose pump assembly in a bottle with a clear cap. One and two actuations of Zolpimist (zolpidem tartrate) Oral Spray deliver 5 and 10 mg of zolpidem tartrate, respectively. There are 30 metered actuations in the 4.5 mL-filled container and 60 metered actuations, after 5 initial priming actuations. Zolpimist (zolpidem tartrate) Oral Spray is supplied as:

NDC Number
69654-0510-30
and,
Size
Carton includes a child-resistant container with 4.5 mL (4.8 g) of product formulation; 30 metered actuations per container.

NDC Number
69654-0510-60
Size
Carton includes a child-resistant container with 7.7 mL (8.2 g) of product formulation; 60 metered actuations per container.

Store upright at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (*USP* Controlled Room Temperature). Do not freeze. Avoid prolonged product exposure to temperatures above 30 °C (86 °F). The child-resistant container should be discarded when the labeled number of actuations (30 or 60 sprays) have been used.

KEEP OUT OF REACH OF CHILDREN.

16 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide): Inform patients and their families about the benefits and risks of treatment with Zolpimist (zolpidem tartrate) Oral Spray. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with Zolpimist (zolpidem tartrate) Oral Spray and with each prescription refill. Review the Zolpimist (zolpidem tartrate) Oral Spray Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that Zolpimist (zolpidem tartrate) Oral Spray should be taken only as prescribed.

CNS depressant effects and next-day impairment: Tell patients that Zolpimist (zolpidem tartrate) Oral Spray has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness. Inform patients that impairment can be present despite feeling fully awake.

Severe anaphylactic and anaphylactoid reactions: Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

Sleep-driving and other complex behaviors: Instruct patients and their families that sedative hypnotics can cause abnormal thinking and behavior change, including “sleep driving” and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex). Tell patients to call their healthcare provider immediately if they develop any of these symptoms.

Suicide: Tell patients to immediately report any suicidal thoughts.

Alcohol and other drugs: Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use Zolpimist (zolpidem tartrate) Oral Spray if they drank alcohol that evening or before bed.

Tolerance, abuse, and dependence: Tell patients not to increase the dose of Zolpimist (zolpidem tartrate) Oral Spray on their own, and to inform their healthcare provider if they believe the drug “does not work.”

Administration instructions: See the Dosage and Administration section *[see Administration (2.4)]*. Zolpimist (zolpidem tartrate) Oral Spray is packaged in a child-resistant container. Patients should be referred to the Patient Instructions for Use (following the Medication Guide) for detailed instructions on how to use Zolpimist (zolpidem tartrate) Oral Spray. Patients should be counseled to take Zolpimist (zolpidem tartrate) Oral Spray right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Zolpimist (zolpidem tartrate) Oral Spray should not be taken with or immediately after a meal. Advise patients NOT to take Zolpimist (zolpidem tartrate) Oral Spray if they drank alcohol that evening.

MEDICATION GUIDE

Zolpimist (zolpidem tartrate) Oral Spray (Zol-pi-mist) [zolpidem tartrate oral spray (C-IV)]

Read the Medication Guide that comes with Zolpimist (zolpidem tartrate) Oral Spray before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Zolpimist (zolpidem tartrate) Oral Spray?

- **Do not take more Zolpimist (zolpidem tartrate) Oral Spray than prescribed.**
- **Do not take Zolpimist (zolpidem tartrate) Oral Spray unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**

Take Zolpimist (zolpidem tartrate) Oral Spray right before you get in bed, not sooner. Zolpimist (zolpidem tartrate) Oral Spray may cause serious side effects including:

- After taking Zolpimist (zolpidem tartrate) Oral Spray, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with Zolpimist (zolpidem tartrate) Oral Spray. Reported activities include:
- driving a car ("sleep-driving")
- making and eating food
- talking on the phone
- having sex
- sleep-walking

Call your healthcare provider right away if you find out that you have done any of the above activities after taking Zolpimist (zolpidem tartrate) Oral Spray. Do not take Zolpimist (zolpidem tartrate) Oral Spray if you:

- drank alcohol that evening or before bed
- took another medicine to help you sleep

What is Zolpimist (zolpidem tartrate) Oral Spray?

Zolpimist (zolpidem tartrate) Oral Spray is a sedative-hypnotic (sleep) medicine. Zolpimist (zolpidem tartrate) Oral Spray is used in adults for the short-term treatment of a sleep problem called insomnia (trouble falling asleep).

It is not known if Zolpimist (zolpidem tartrate) Oral Spray is safe and effective in children under the age of 18 years.

Zolpimist (zolpidem tartrate) Oral Spray is a federally controlled substance (C-IV) because it can be abused and lead to dependence. Keep Zolpimist (zolpidem tartrate) Oral Spray in a safe place to prevent misuse and abuse. Selling or giving away Zolpimist (zolpidem tartrate) Oral Spray may harm others, and is against the law. Tell your healthcare provider if you have ever abused or have been dependent on alcohol, prescription medicines, or street drugs.

Who should not take Zolpimist (zolpidem tartrate) Oral Spray?

- Do not take Zolpimist (zolpidem tartrate) Oral Spray if you are allergic to zolpidem or any other ingredients in Zolpimist (zolpidem tartrate) Oral Spray. See the end of this Medication Guide for a complete list of ingredients in Zolpimist (zolpidem tartrate) Oral Spray.
- Do not take Zolpimist (zolpidem tartrate) Oral Spray if you have had an allergic reaction to zolpidem, such as Ambien, Ambien CR, Edluar, or Intermezzo. Symptoms of a serious allergic reaction to zolpidem can include: swelling of your face, lips, and throat that may cause difficulty breathing or swallowing.

What should I tell my healthcare provider before taking Zolpimist (zolpidem tartrate) Oral Spray?

Zolpimist (zolpidem tartrate) Oral Spray may not be right for you. Before starting Zolpimist (zolpidem tartrate) Oral Spray, tell your healthcare provider about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts.
- have a history of drug or alcohol abuse or addiction.
- have kidney or liver disease.
- have a lung disease or breathing problems.
- are pregnant, planning to become pregnant. It is not known if Zolpimist (zolpidem tartrate) Oral Spray will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Zolpimist (zolpidem tartrate) Oral Spray can pass into your breast milk. It is not known if Zolpimist (zolpidem tartrate) Oral Spray will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take Zolpimist (zolpidem tartrate) Oral Spray.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Medicines can interact with each other, sometimes causing serious side effects. **Do not take Zolpimist (zolpidem tartrate) Oral Spray with other medicines that can make you sleepy unless your healthcare provider tells you to**.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take Zolpimist (zolpidem tartrate) Oral Spray?

- See **"What is the most important information I should know about Zolpimist (zolpidem tartrate) Oral Spray?"**
- Take Zolpimist (zolpidem tartrate) Oral Spray exactly as prescribed. Only take 1 Zolpimist (zolpidem tartrate) Oral Spray dose a night if needed.
- Do not take Zolpimist (zolpidem tartrate) Oral Spray if you drank alcohol that evening or before bed.
- You should not take Zolpimist (zolpidem tartrate) Oral Spray with or right after a meal. Zolpimist (zolpidem tartrate) Oral Spray may help you fall asleep faster if you take it on an empty stomach.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- If you take too much Zolpimist (zolpidem tartrate) Oral Spray or overdose, get emergency treatment.

What are the possible side effects of Zolpimist (zolpidem tartrate) Oral Spray? Zolpimist (zolpidem tartrate) Oral Spray may cause serious side effects, including:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** See "**What is the most important information I should know about Zolpimist (zolpidem tartrate) Oral Spray?**"
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, and trouble breathing. Get emergency medical help if you get these symptoms after taking Zolpimist (zolpidem tartrate) Oral Spray.

Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using Zolpimist (zolpidem tartrate) Oral Spray.

The most common side effects of Zolpimist (zolpidem tartrate) Oral Spray are:

- drowsiness
- dizziness
- diarrhea
- grogginess or feeling as if you have been drugged

After you stop taking a sleep medicine, you may have symptoms for 1 or 2 days such as:

• trouble sleeping	• vomiting
• nausea	• stomach cramps
• flushing	• panic attack
• lightheadedness	• nervousness
• uncontrolled crying	• stomach area pain

These are not all the side effects of Zolpimist (zolpidem tartrate) Oral Spray. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Aytu BioScience, Inc. at 1-855-298-8246.

How should I store Zolpimist (zolpidem tartrate) Oral Spray?
- Store Zolpimist (zolpidem tartrate) Oral Spray in an upright position between 59 °F to 86 °F (15 °C to 30 °C).
- Do not freeze.
- Avoid prolonged product exposure above 86 °F (30 °C).
- The child-resistant container should be thrown away when the 30 or 60 sprays have been used, depending upon the package size (4.5 mL; 30 sprays or 7.7 mL; 60 sprays).

Keep Zolpimist (zolpidem tartrate) Oral Spray and all medicines out of reach of children.

General information about safe and effective use of Zolpimist (zolpidem tartrate) Oral Spray
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use Zolpimist (zolpidem tartrate) Oral Spray for a condition for which it was not prescribed.

Do not share Zolpimist (zolpidem tartrate) Oral Spray with other people, even if they may have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about Zolpimist (zolpidem tartrate) Oral Spray. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Zolpimist (zolpidem tartrate) Oral Spray that is written for healthcare professionals.

For more information about Zolpimist (zolpidem tartrate) Oral Spray, call 1-855-298-8246.

What are the ingredients in Zolpimist (zolpidem tartrate) Oral Spray?
Active ingredient: Zolpidem tartrate

Inactive ingredients: artificial cherry flavor, benzoic acid, citric acid monohydrate, hydrochloric acid, neotame, propylene glycol, and purified water.

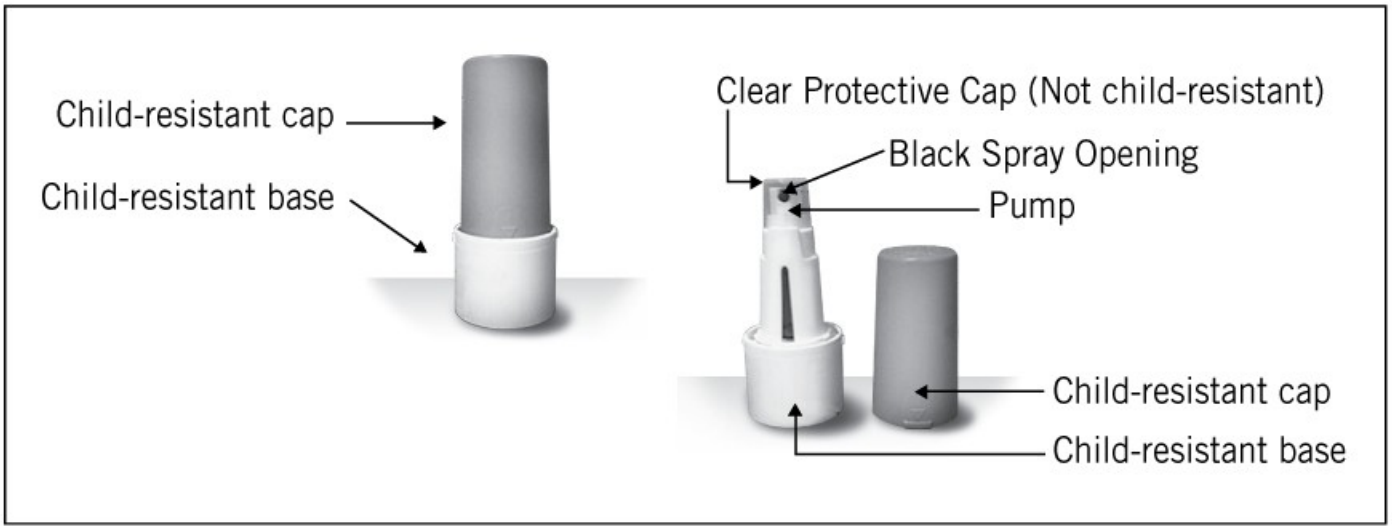
This Medication Guide has been approved by U.S. Food and Drug Administration.

Aytu BioScience, Inc.
373 Inverness Pkwy, Suite 206
Englewood, CO 80112

January 2016

Patient Instructions for Use
Zolpimist (zolpidem tartrate)
Oral Spray, Metered for Oral Use

Be sure to carefully read, understand, and follow these instructions so that you use Zolpimist (zolpidem tartrate) Oral Spray the right way. Ask your healthcare provider or pharmacist if you have any questions about how to use Zolpimist (zolpidem tartrate) Oral Spray.



Priming:
Before you use Zolpimist (zolpidem tartrate) Oral Spray for the first time or if you have not used Zolpimist (zolpidem tartrate) Oral Spray for 14 days, you will need to prime the pump (Steps 1-6). Otherwise, go directly to Step 7.

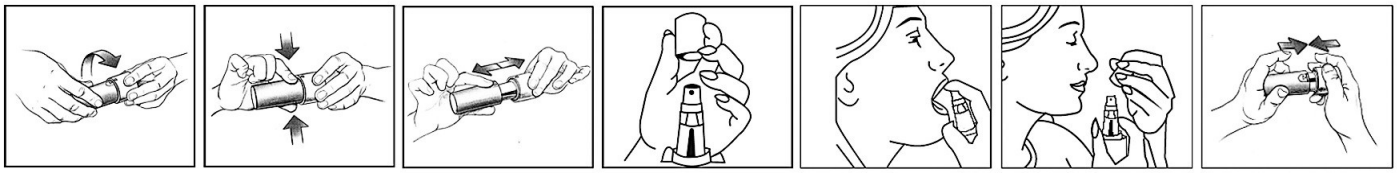
To prime the pump:
1. Line up the arrows on the child-resistant cap and base (see Figure 1).
2. Squeeze the cap at arrows (see Figure 2).
3. Pry the cap and base to separate (see Figure 3).
4. Remove the clear protective cap from the pump (see Figure 4).
5. Hold the container upright. Point the black spray opening in a safe direction away from your face and other people. Fully press down on the pump with your forefinger. Release the pump and let the pump return to the starting position.
6. Follow step 5 and press down on the pump 4 more times. You should see a fine spray. Zolpimist (zolpidem tartrate) Oral Spray is now ready to use. Now go directly to Step 11.

Taking a dose of Zolpimist (zolpidem tartrate) Oral Spray:
- **If you are using Zolpimist (zolpidem tartrate) Oral Spray for the first time or you have not used Zolpimist (zolpidem tartrate) Oral Spray for 14 days, you will need to prime the pump (Steps 1-6). Otherwise, there is no need to prime the pump.**
- **Take Zolpimist (zolpidem tartrate) Oral Spray exactly as prescribed. Do not take more Zolpimist (zolpidem tartrate) Oral Spray than prescribed for you.** Your healthcare provider will tell you whether to take 1 or 2 sprays of Zolpimist (zolpidem tartrate) Oral Spray.
- **Take Zolpimist (zolpidem tartrate) Oral Spray right before you get into bed.**
- **Do not take Zolpimist (zolpidem tartrate) Oral Spray unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**

7. Line up the arrows on the child-resistant cap and base (see Figure 1).
8. Squeeze the cap at arrows (see Figure 2).
9. Pull the cap and base to separate (see Figure 3).
10. Remove the clear protective cap from the pump (see Figure 4).
11. Hold the container upright with the black spray opening pointed directly into your mouth. Fully press down on the pump to make sure that a full dose of Zolpimist (zolpidem tartrate) Oral Spray is sprayed directly into your open mouth over your tongue (see Figure 5).
12. Let the pump return to the starting position. If your healthcare provider prescribed only one spray of Zolpimist (zolpidem tartrate) Oral Spray (5 mg dose), go directly to Step 14.
13. If your healthcare provider prescribes a second spray of Zolpimist (zolpidem tartrate) Oral Spray (10 mg dose), repeat Step 11.
14. Put the clear protective cap back over the pump at the top of the child-resistant base after each use (see Figure 6).

15. Snap the child-resistant cap back onto the base and rotate the child-resistant cap and the child-resistant base so that the arrows are not lined up (see Figure 7).
16. The child-resistant container should be thrown away when the 60 sprays have been used.

FIGURE 1 **FIGURE 2** **FIGURE 3** **FIGURE 4** **FIGURE 5** **FIGURE 6** **FIGURE 7**



There are no special requirements for cleaning and maintaining Zolpimist (zolpidem tartrate) Oral Spray. Professional assistance regarding questions about product performance or use can be obtained by calling 1-855-298-8246.

See Medication Guide section "How should I store Zolpimist (zolpidem tartrate) Oral Spray?" for instructions about how to store Zolpimist (zolpidem tartrate) Oral Spray.

Manufactured for:

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by

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