

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-196

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zolpimist safely and effectively. See full prescribing information for Zolpimist (zolpidem tartrate) Oral Spray 

Initial U.S. Approval: 1992

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. (1)

DOSAGE AND ADMINISTRATION

- Adult dose: 10 mg once daily immediately before bedtime. (2.1)
- Elderly/debilitated patients/hepatic impaired: 5 mg once daily immediately before bedtime. (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants. (2.3)
- Should not be taken with or immediately after a meal. (2.4)

DOSAGE FORMS AND STRENGTHS

Each metered actuation (one spray) of Zolpimist delivers 5 mg of zolpidem tartrate in 100 µL. After an initial priming of 5 actuations, there are 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 tartrate.

WARNINGS AND PRECAUTIONS

- Need to evaluate for co-morbid diagnosis: Reevaluate if insomnia persists after 7 to 10 days of use. (5.1)
- Severe anaphylactic and anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.2)
- Abnormal thinking, behavioral changes, and complex behaviors: May include "sleep-driving" and hallucinations. Immediately evaluate any new onset of behavioral changes. (5.3)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose. (5.3, 5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.4, 9.3)

- CNS-depressant effects: Use can impair alertness and motor coordination. If used in combination with other CNS depressants, dose reduction may be needed due to additive effects. Do not use with alcohol. (2.3, 5.5)
- Elderly/debilitated patients: Use lower dose due to impaired motor, cognitive performance, and increased sensitivity. (2.2, 5.6)
- Patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, mild to moderate sleep apnea: Use with caution and monitor closely. (5.6)

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 NovaDel Pharma Inc. at 1-800- and <http://www.novadel.com> or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

DRUG INTERACTIONS

- CNS depressants: Enhanced CNS-depressant effects with combination use. Use with alcohol causes additive psychomotor impairment. (7.1)
- Imipramine: Decreased alertness observed with combination use. (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed with combination use. (7.1)
- Rifampin: Combination use decreases exposure to and effects of zolpidem. (7.2)
- Ketoconazole: Combination use increases exposure to and effect of zolpidem. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm. (8.1)
- Nursing mothers: Infant exposure via breast milk. (8.3)
- Pediatric use: Safety and effectiveness have not been established. Hallucinations (incidence rate 7.4%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder. (5.6, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/08

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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

The dose of Zolpimist should be individualized.

2.1 Dosage in adults

The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Zolpimist dose should not exceed 10 mg per day.

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 in both of these patient populations is 5 mg once daily immediately before bedtime [see *Warnings and Precautions (5.6)*].

2.3 Use with CNS depressants

Dosage adjustment may be necessary when Zolpimist is combined with other CNS-depressant drugs because of the potentially additive effects [see *Warnings and Precautions (5.5)*].

2.4 Administration

Zolpimist is packaged in a child-resistant container. For detailed instructions on how to use Zolpimist, refer to the Patient Instructions for Use (following the Medication Guide). Zolpimist 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 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 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 may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Zolpimist 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 delivers 5 mg of zolpidem tartrate in 100 μ L. Two actuations deliver 10 mg of zolpidem tartrate.

After an initial priming of 5 actuations, there are 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.

4 CONTRAINDICATIONS

Known hypersensitivity to zolpidem tartrate [*see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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 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.

5.3 Abnormal thinking and behavioral changes

A variety of abnormal thinking and behavioral changes have been reported to occur in association with the use of sedative-hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation, and depersonalization. In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem, reported hallucinations [*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 with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with Zolpimist alone at therapeutic doses, the use of alcohol and other CNS depressants with zolpidem tartrate appears to increase the risk of such behaviors, as does the use of zolpidem at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Zolpimist 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 occur unpredictably.

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of sedative-hypnotics.

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

5.4 Withdrawal effects

Following the rapid dose decrease or abrupt discontinuation of sedative-hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs [*see Drug Abuse and Dependence (9)*].

5.5 CNS-depressant effects

Zolpidem tartrate, like other sedative-hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Zolpimist should only be administered 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, including potential impairment of the performance of such activities that may occur the day following administration of Zolpimist. Zolpidem tartrate showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Zolpimist is administered with such agents because of the potentially additive effects.

5.6 Special populations

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative-hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Zolpimist dosage is 5 mg in such patients to decrease the possibility of side effects [*see Dosage and Administration (2.2)*]. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with zolpidem tartrate in patients with concomitant systemic illness is limited. Caution is advisable in using Zolpimist in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem in normal 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 tartrate (10 mg) when

compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Zolpimist is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Zolpimist should be used with caution in patients with sleep apnea syndrome or myasthenia gravis.

Data in end-stage renal failure patients repeatedly treated with zolpidem tartrate did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored [see *Clinical Pharmacology (12.3)*].

A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

Use in patients with depression: As with other sedative-hypnotic drugs, Zolpimist should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional over-dosage 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.

Use in pediatric patients: Safety and effectiveness of zolpidem have not been established in pediatric patients. In an 8-week study in pediatric patients (6-17 years of age) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem tartrate; none of the pediatric patients who received placebo reported hallucinations [see *Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

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

- Serious anaphylactic and anaphylactoid reactions [see *Warnings and Precautions (5.2)*].
- Abnormal thinking, behavior changes, and complex behaviors [see *Warnings and Precautions (5.3)*].
- Withdrawal effects [see *Warnings and Precautions (5.4)*].
- CNS-depressant effects [see *Warnings and Precautions (5.5)*].

6.1 Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating incidence rates.

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 $\geq 1\%$ in controlled trials: The following tables enumerate treatment-emergent adverse reactions 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 pharmacokinetics studies: The effect of chronic daily administrations of Zolpimist on oral tissue has not been evaluated. In pharmacokinetic studies conducted with Zolpimist 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.

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 event 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. Infrequent: bronchitis, coughing, dyspnea, rhinitis. Rare: bronchospasm, 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

Since the systematic evaluations of zolpidem in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with Zolpimist. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Zolpidem tartrate was evaluated in healthy subjects 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 tartrate 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 a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated [*see Warnings and Precautions (5.5)*].

A single-dose interaction study with zolpidem 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 at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life ($t_{1/2}$). There was no evidence of an additive effect in psychomotor performance.

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

7.2 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 has not been carefully evaluated.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female subjects between five consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last dose of rifampin 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.

A randomized double-blind crossover interaction study in twelve healthy subjects showed that co-administration of single 5 mg dose of zolpidem tartrate with ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem by a factor of 1.3 and increased the total AUC of zolpidem by a factor of 1.7 compared to zolpidem alone and prolonged the $t_{1/2}$ by approximately 30% along with an increase in the pharmacodynamic effects of zolpidem. Caution should be used when ketoconazole is given with zolpidem and consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together. Patients should be advised that use of Zolpimist with ketoconazole may enhance the sedative effects.

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 screen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born to mothers taking sedative-hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition,

neonatal flaccidity has been reported in infants born of mothers who received sedative-hypnotic drugs during pregnancy.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 10 mg/day (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 (≈ 5 , 24, and 120 times the MRHD on a mg/m^2 basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification were observed at all but the low dose, which is 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 (≈ 2.5 , 10, and 40 times the MRHD on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification were seen at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is ≈ 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 (≈ 5 , 24, and 120 times the MRHD on a mg/m^2 basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the low dose, which is ≈ 5 times the MRHD on a mg/m^2 basis.

8.2 Labor and delivery

Zolpimist has no established use in labor and delivery [*see Pregnancy (8.1)*].

8.3 Nursing mothers

Zolpidem is excreted into human milk. Studies in lactating mothers indicate that the $t_{1/2}$ of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hours). Between 0.004% and 0.019% of the total administered dose is excreted into milk. The effect of zolpidem on the nursing infant is not known.

8.4 Pediatric use

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (6-17 years of age) with insomnia associated with ADHD (90% of the patients were using psychoanaleptics) were treated with an oral solution of zolpidem ($n=136$) or placebo ($n=65$). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent ($> 5\%$) treatment emergent adverse reactions observed with zolpidem tartrate versus placebo and included dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations (7.4% vs 0%) [*see Warnings and Precautions (5.6)*]. 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 zolpidem were ≥ 60 years of age. In a pool of U.S. patients receiving zolpidem at doses of ≤ 10 mg or placebo, there were three adverse reactions occurring at an incidence of at