ZOLPIDEM TARTRATE- zolpidem tartrate tablet, film coated
Lake Erie Medical DBA Quality Care Products LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use zolpidem tartrate tablets safely and effectively. See full prescribing information for zolpidem tartrate tablets

Zolpidem tartrate tablets

CIV

Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Indications and Usage (1) 03/2007
Warnings and Precautions
Severe anaphylactic and anaphylactoid reactions (5.2) 03/2007
Abnormal thinking and behavioral changes (5.3) 03/2007
Special populations (5.6) 03/2007

INDICATIONS AND USAGE

Zolpidem tartrate tablets are indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate tablets have 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/hepatically 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

5 mg and 10 mg tablets. Tablets not scored (3)

CONTRAINDICATIONS

Known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation (4)

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/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 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 reductions 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 Vintage Pharmaceuticals, LLC at 1-800-444-4011 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 effects of zolpidem (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm (8.1)
- Nursing mothers: Zolpidem is excreted in human milk (8.3)

- Pediatric use: Safety and effectiveness not 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: 9/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage in adults
2.2 Special populations
2.3 Use with CNS depressants
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Need to evaluate for co-morbid diagnoses
5.2 Severe anaphylactic and anaphylactoid reactions
5.3 Abnormal thinking and behavioral changes
5.4 Withdrawal effects
5.5 CNS depressant effects
5.6 Special populations
6 ADVERSE REACTIONS
6.1 Clinical trials experience
7 DRUG INTERACTIONS
7.1 CNS-active drugs
7.2 Drugs that affect drug metabolism via cytochrome P450
7.3 Other drugs with no interaction with zolpidem
7.4 Drug-laboratory test interactions
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and delivery
8.3 Nursing mothers
8.4 Pediatric use
8.5 Geriatric use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Signs and symptoms
10.2 Recommended treatment
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, mutagenesis, impairment of fertility
14 CLINICAL STUDIES
14.1 Transient insomnia
14.2 Chronic insomnia
14.3 Studies pertinent to safety concerns for sedative/hypnotic drugs
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Severe anaphylactic and anaphylactoid reactions
17.2 Sleep-driving and other complex behaviors

17.3 Administration instructions
17.4 Medication Guide
* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zolpidem tartrate tablets are indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate tablets have 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 zolpidem tartrate tablets should be individualized.

2.1 Dosage in adults

The recommended dose for adults is 10 mg once daily immediately before bedtime. The total zolpidem tartrate tablet 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 zolpidem tartrate 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 zolpidem tartrate tablets are combined with other CNS depressant drugs because of the potentially additive effects *[see Warnings and Precautions (5.5)]*.

2.4 Administration

The effect of zolpidem tartrate tablets may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Zolpidem tartrate tablets are available in 5 mg and 10 mg strength tablets for oral administration. Tablets are not scored.

Zolpidem tartrate tablets 5 mg are pink, film-coated, capsule-shaped, unscored, upper debossed "6468" and lower debossed "V". The 10 mg tablets are white, film-coated, capsule-shaped, unscored, upper debossed "6469" and lower debossed "V".

4 CONTRAINDICATIONS

Zolpidem tartrate tablets are contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation. Observed reactions include anaphylaxis and angioedema *[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 behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including 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 behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that 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-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with zolpidem tartrate tablets alone at therapeutic doses, the use of alcohol and other CNS depressants with zolpidem tartrate tablets appears to increase the risk of such behaviors, as does the use of zolpidem tartrate tablets at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of zolpidem tartrate tablets 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 neuro-psychiatric 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 tablets, like other sedative/hypnotic drugs, have CNS-depressant effects. Due to the rapid onset of action, zolpidem tartrate tablets should only be taken 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 ingestion of zolpidem tartrate tablets. Zolpidem tartrate tablets 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 zolpidem tartrate tablets are 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 zolpidem tartrate tablets 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 tablets in patients with concomitant systemic illness is limited. Caution is advisable in using zolpidem tartrate tablets 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 tablets (10 mg) when compared to placebo. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be taken if zolpidem tartrate tablets are prescribed to patients with compromised respiratory function. Postmarketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Zolpidem tartrate tablets 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 tablets 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, zolpidem tartrate tablets 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 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.

Use in pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6–17 years) 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; 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

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem 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 tablets 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 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 Experiences in Placebo-Controlled Clinical Trials Lasting up to 10 Nights

	(Percentage of patients reporting)	
Body System/ Adverse Event	Zolpidem (≤10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	-

The following table was derived from results of three placebo-controlled long-term efficacy trials involving zolpidem tartrate tablets. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem 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 events occurring at an incidence of at least 1% for zolpidem patients.

Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials Lasting up to 35 Nights

	(Percentage of patients reporting)	
Body System/ Adverse Event	Zolpidem (≤10 mg) (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

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 use, particularly for certain CNS and gastrointestinal adverse events.

Adverse event incidence across the entire preapproval database: Zolpidem tartrate tablets were administered to 3,660 subjects in clinical trials throughout the U.S., 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 World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. 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 tablets, 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, tendinitis.

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 zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Zolpidem tartrate tablets were 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 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. 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 C_{max} was significantly higher (43%) and 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 $T_{½}$ (-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 a 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 elimination half-life 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 zolpidem tartrate tablets 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 screens.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well-controlled studies of zolpidem tartrate tablets in pregnant women.

Zolpidem tartrate tablets 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 approximately 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 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 (approximately 2.5, 10 and 40 times the MRHD on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. 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 (approximately 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 lowest dose, which is approximately 5 times the MRHD on a mg/m^2 basis.

Neonatal Complications
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 some 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.

8.2 Labor and delivery

Zolpidem tartrate tablets have no established use in labor and delivery *[see Pregnancy (8.1)]*.

8.3 Nursing mothers

Zolpidem is excreted in human milk. Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hr). The effect of zolpidem on the nursing infant is not known. Caution should be exercised when zolpidem tartrate tables are administered to a nursing woman.

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 (aged 6–17 years) with insomnia associated with attention-deficit/hyperactivity disorder (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 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. For 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 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 Event	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 zolpidem tartrate tablets in elderly patients is 5 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs *[see Warnings and Precautions (5.6)]*.

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 events 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 events 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

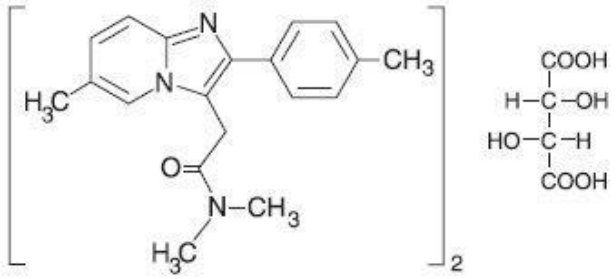
where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of 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

Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class and is available in 5 mg and 10 mg strength tablets for oral administration.

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 764.88.

Each zolpidem tartrate tablet includes the following inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide; the 5-mg tablet also contains FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, polyethylene glycol, polyvinyl alcohol, and talc; the 10-mg tablet also contains stearic acid and triacetin.

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 nonselectively 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 tartrate at hypnotic doses.

12.3 Pharmacokinetics

The pharmacokinetic profile of zolpidem tartrate tablets is characterized by rapid absorption from the gastrointestinal tract and a short elimination half-life ($T_{½}$) in healthy subjects.

In a single-dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean zolpidem tartrate

tablets elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. Zolpidem tartrate tablets are converted to inactive metabolites that are eliminated primarily by renal excretion. Zolpidem tartrate tablets demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding 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 tablets for 2 weeks.

A food-effect study in 30 healthy male subjects compared the pharmacokinetics of zolpidem tartrate tablets 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, zolpidem tartrate tablets should not be administered with or immediately after a meal.

Special Populations
Elderly:
In the elderly, the dose for zolpidem tartrate tablets 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}, $T_{½}$, and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (>70 years), the means for C_{max}, $T_{½}$, and AUC significantly increased by 50% (255 vs. 384 ng/mL), 32% (2.2 vs. 2.9 hr), and 64% (955 vs. 1,562 ng·hr/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20 mg oral dose. Zolpidem tartrate tablets did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Hepatic Impairment:
The pharmacokinetics of zolpidem tartrate tablets 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 half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)]*.

Renal Impairment:
The pharmacokinetics of zolpidem tartrate 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}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{½}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{½}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. 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. However, as a general precaution, these patients should be closely monitored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis:
Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. 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 or approximately 5, 24, and 120 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. 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 tartrate tablets.

14.3 Studies pertinent to safety concerns for sedative/hypnotic drugs

Next-day residual effects: Next-day residual effects of zolpidem tartrate tablets 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 tablets in nonelderly 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 tablets. 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 tablets. 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 tablets, 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 tablets have 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Zolpidem Tartrate Tablets are available as:

5 mg, pink, film-coated, capsule-shaped, unscored, debossed "6468" on one side and debossed "V" on the reverse side, in bottles of 10, 20, 30, 100, 500 and 1000.

10 mg, white, film-coated, capsule-shaped, unscored, debossed "6469" on one side and debossed "V" on the reverse side, in bottles of 10, 15, 20, 30, 60, 90, 100, 500 and 1000.

Store at controlled room temperature 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics, should counsel them in its appropriate use, and should instruct them to read the accompanying Medication Guide *[see Medication Guide (17.4)]*.

17.1 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.

17.2 Sleep-driving and other complex behaviors

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when zolpidem tartrate tablets are taken with alcohol or other central nervous system depressants *[see Warnings and Precautions (5.3)]*. 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.

In addition, patients should be advised to report all concomitant medications to the prescriber. Patients should be instructed to report events such as "sleep-driving" and other complex behaviors immediately to the prescriber.

17.3 Administration instructions

Patients should be counseled to take zolpidem tartrate tablets 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. Zolpidem tartrate tablets should not be taken with or immediately after a meal. Advise patients NOT to take zolpidem tartrate tablets when drinking alcohol.

17.4 Medication Guide

MEDICATION GUIDE
ZOLPIDEM TARTRATE TABLETS

Read the Medication Guide that comes with zolpidem tartrate tablets 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 doctor about your medical condition or treatment.

What is the most important information I should know about zolpidem tartrate tablets?

After taking zolpidem tartrate tablets, 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 zolpidem tartrate tablets. Reported activities include:

- driving a car ("sleep-driving")
- making and eating food
- talking on the phone
- having sex
- sleep-walking

Call your doctor right away if you find out that you have done any of the above activities after taking zolpidem tartrate tablets.

Important:

1. Take zolpidem tartrate tablets exactly as prescribed

- Do not take more zolpidem tartrate tablets than prescribed.
- Take zolpidem tartrate tablets right before you get in bed, not sooner.

2. Do not take zolpidem tartrate tablets if you:

- drink alcohol
- take other medicines that can make you sleepy. Talk to your doctor about all of your medicines. Your doctor will tell you if you can take zolpidem tartrate tablets with your other medicines.
- cannot get a full night's sleep

What is zolpidem tartrate tablets?

Zolpidem tartrate tablets is a sedative-hypnotic (sleep) medicine.

Zolpidem tartrate tablets is used in adults for the short-term treatment of a sleep problem called insomnia.

Symptoms of insomnia include:

- trouble falling asleep.

Zolpidem tartrate tablets is not for children.

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

Who should not take zolpidem tartrate tablets?

Do not take zolpidem tartrate tablets if you are allergic to anything in it.

See the end of this Medication Guide for a complete list of ingredients in zolpidem tartrate tablets.

Zolpidem tartrate tablets may not be right for you. Before starting zolpidem tartrate tablets, tell your doctor 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, or breastfeeding

Tell your doctor about all of 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 zolpidem tartrate tablets with other medicines that can make you sleepy.**

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

How should I take zolpidem tartrate tablets?

- Take zolpidem tartrate tablets exactly as prescribed. Do not take more zolpidem tartrate tablets than

prescribed for you.

- **Take zolpidem tartrate tablets right before you get into bed.**
- **Do not take zolpidem tartrate tablets unless you are able to stay in bed a full night (7–8 hours) before you must be active again.**
- For faster sleep onset, zolpidem tartrate tablets should NOT be taken with or immediately after a meal.
- Call your doctor 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 zolpidem tartrate tablets or overdose, call your doctor or poison control center right away, or get emergency treatment.

What are the possible side effects of zolpidem tartrate tablets?

Serious side effects of zolpidem tartrate tablets include:

- **getting out of bed while not being fully awake and do an activity that you do not know you are doing.** (See "What is the most important information I should know about zolpidem tartrate tablets?")
- **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, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking zolpidem tartrate tablets.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using zolpidem tartrate tablets.

The most common side effects of zolpidem tartrate tablets are:

- drowsiness
- dizziness
- diarrhea
- "drugged feelings"
- You may still feel drowsy the next day after taking zolpidem tartrate tablets. **Do not drive or do other dangerous activities after taking zolpidem tartrate tablets until you feel fully awake.**

After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as: trouble sleeping, nausea, flushing, lightheadedness, uncontrolled crying, vomiting, stomach cramps, panic attack, nervousness, and stomach area pain.

These are not all the side effects of zolpidem tartrate tablets. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store zolpidem tartrate tablets?

- Store zolpidem tartrate tablets at room temperature, 68° to 77°F (20° to 25°C).
- **Keep zolpidem tartrate tablets and all medicines out of reach of children.**

General information about zolpidem tartrate tablets

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use zolpidem tartrate tablets for a condition for which it was not prescribed.
- Do not share zolpidem tartrate tablets with other people, even if you think they 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 zolpidem tartrate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about zolpidem tartrate tablets that is written for healthcare professionals.

What are the ingredients in zolpidem tartrate tablets?

Active ingredient: Zolpidem tartrate

Inactive Ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide; the 5-mg tablet also contains FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, polyethylene glycol, polyvinyl alcohol, and talc; the 10-mg tablet also contains stearic acid and triacetin.

Rx Only

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

Manufactured for:
QUALITEST PHARMACEUTICALS
Huntsville, AL 35811

8182348
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R2

A SUPPLY OF MEDICATION GUIDES AS PRINTED AT THE END OF THIS INSERT IS AVAILABLE, FREE OF CHARGE, BY CALLING
(800) 444-4011.

MEDICATION GUIDE

CIV

ZOLPIDEM TARTRATE TABLETS

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- driving a car ("sleep-driving")
- making and eating food
- talking on the phone
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- sleep-walking

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- have a lung disease or breathing problems
- are pregnant, planning to become pregnant, or breastfeeding

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- Call your doctor 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 zolpidem tartrate tablets or overdose, call your doctor or poison control center right away, or get emergency treatment.

What are the possible side effects of zolpidem tartrate tablets?

Serious side effects of zolpidem tartrate tablets include:
- **getting out of bed while not being fully awake and do an activity that you do not know you are doing.** (See "What is the most important information I should know about zolpidem tartrate tablets?")
- **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, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking zolpidem tartrate tablets.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using zolpidem tartrate tablets.

The most common side effects of zolpidem tartrate tablets are:

- drowsiness
- dizziness
- diarrhea
- "drugged feelings"
- You may still feel drowsy the next day after taking zolpidem tartrate tablets. **Do not drive or do other dangerous activities after taking zolpidem tartrate tablets until you feel fully awake.**

After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as: trouble sleeping, nausea, flushing, lightheadedness, uncontrolled crying, vomiting, stomach cramps, panic attack, nervousness, and stomach area pain.

These are not all the side effects of zolpidem tartrate tablets. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store zolpidem tartrate tablets?

- Store zolpidem tartrate tablets at room temperature, 68° to 77°F (20° to 25°C).
- **Keep zolpidem tartrate tablets and all medicines out of reach of children.**

General information about zolpidem tartrate tablets

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use zolpidem tartrate tablets for a condition for which it was not prescribed.
- Do not share zolpidem tartrate tablets with other people, even if you think they 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 zolpidem tartrate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about zolpidem tartrate tablets that is written for healthcare professionals.

What are the ingredients in zolpidem tartrate tablets?

Active ingredient: Zolpidem tartrate

Inactive Ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide; the 5-mg tablet also contains FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, polyethylene glycol, polyvinyl alcohol, and talc; the 10-mg tablet also contains stearic acid and triacetin.

Rx Only

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

Manufactured for:
QUALITEST PHARMACEUTICALS
Huntsville, AL 35811

8182493
Revised: 1/2009
R0

image of label

Packaged and Distributed by Quality Care Products, LLC 1-800-337-8603

Temperance, MI 48182

ZOLPIDEM TARTRATE 5 MG

30 TABLETS

Each tablet contains Zolpidem Tartrate 5 mg
polyvinyl alcohol

WARNING: MAY BE HABIT FORMING

Lot:
Exp:
REV.

Item # 0068183FL
NDC: 49999-0932-30

Mfr. for: QUALITEST PHARMACEUTICALS, Huntsville, AL 35811

Take_____tablet(s) every_____hours or_____time(s) a day.
Take as directed.
Tome_____tableta(s) cada_____horas o_____vece(s) al dia.
Tome como indicado.

Rx only

CIV

PINK, FILM-COATED, CAPSULE-SHAPED, UNSCORED, DEBOSSED "6468" ON ONE SIDE AND DEBOSSED "V" ON THE REVERSE SIDE

Warning: Keep out of children's reach.
Dispense in this tight/light resistant container.
Store at controlled temperature 68-77 degrees F.
Caution: Do not use with alcohol
without consulting a physician

ZOLPIDEM TARTRATE 5 MG
30 TABLETS
Lot:
Exp:
NDC: 49999-0932-30
Rx #: 0000053509

ZOLPIDEM TARTRATE 5 MG
30 TABLETS
Lot:
Exp:
NDC: 49999-0932-30
Rx #: 0000053509

Rx #: 0000053509

ZOLPIDEM TARTRATE

zolpidem tartrate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:49999-932(NDC:0603-6468)
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ZOLPIDEM TARTRATE (ZOLPIDEM)	ZOLPIDEM TARTRATE	5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE	
HYPROMELLOSES	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
SODIUM STARCH GLYCOLATE TYPE A POTATO	
TITANIUM DIOXIDE	
FD&C BLUE NO. 2	
FD&C RED NO. 40	
POLYETHYLENE GLYCOL 400	
POLYVINYL ALCOHOL	
TALC	

Product Characteristics

Color	pink	**Score**	no score
Shape	OVAL (capsule-shaped)	**Size**	10mm
Flavor		**Imprint Code**	6468;V
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49999-932-30	30 in 1 BOTTLE, PLASTIC		
2	NDC:49999-932-60	60 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078616	11/07/2011	

Labeler - Lake Erie Medical DBA Quality Care Products LLC (831276758)

Establishment

Name	Address	ID/FEI	Business Operations
Lake Erie Medical DBA Quality Care Products LLC		831276758	repack(49999-932)