ZOLPIDEM TARTRATE- zolpidem tartrate tablet, extended release
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use zolpidem tartrate extended-release tablets, USP safely and effectively. See full prescribing information for zolpidem tartrate extended-release tablets, USP.
Zolpidem Tartrate Extended-Release Tablets, USP
Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Indications and Usage (1) 12/2007
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) 04/2007

INDICATIONS AND USAGE

Zolpidem tartrate extended-release tablet, USP is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1) (1)

DOSAGE AND ADMINISTRATION

- Adult dose: 12.5 mg once daily immediately before bedtime (2.1)
- Elderly/debilitated/hepatically impaired patients: 6.25 mg once daily immediately before bedtime (2.2)
- Tablets to be swallowed whole, not to be crushed, divided or chewed. Should not be taken with or immediately after a meal (2.4)

DOSAGE FORMS AND STRENGTHS

6.25 mg and 12.5 mg extended-release tablets, USP. Tablets not scored (3) (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Need to evaluate for co-morbid diagnoses: Revaluate 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, 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, 9.2)
- 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) (5)

- 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 (> 10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or **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: 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.

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zolpidem tartrate extended-release tablet, USP is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) in duration *[see* **CLINICAL STUDIES (14)***]*.

2 DOSAGE AND ADMINISTRATION

The dose of zolpidem tartrate extended-release tablets, USP should be individualized.

2.1 Dosage in Adults

The recommended dose of zolpidem tartrate extended-release tablets for adults is 12.5 mg once daily immediately before bedtime. The total zolpidem tartrate extended-release tablets dose should not exceed 12.5 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 normals. The recommended dose of zolpidem tartrate extended-release tablets in both of these patient populations is 6.25 mg once daily immediately before bedtime *[see* **WARNINGS AND PRECAUTIONS (5.6)***]*.

2.3 Use With CNS Depressants

Dosage adjustments may be necessary when zolpidem tartrate extended-release tablet is combined with other CNS depressant drugs because of the potentially additive effects *[see* **WARNINGS AND PRECAUTIONS (5.5)***]*.

2.4 Administration

Zolpidem tartrate extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of zolpidem tartrate extended-release tablets may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Zolpidem tartrate extended-release tablets, USP containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

Zolpidem tartrate extended-release tablets, 6.25 mg are dark pink, round, biconvex film-coated tablets debossed with SZ on one side and 228 on the other side.

Zolpidem tartrate extended-release tablets, 12.5 mg tablets are light pink, round, biconvex film-coated tablets debossed with SZ on one side and 229 on the other side.

4 CONTRAINDICATIONS

Zolpidem tartrate extended-release tablet is 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 extended-release tablets alone at therapeutic doses, the use of alcohol and other CNS depressants with zolpidem tartrate extended-release tablets appears to increase the risk of such behaviors, as does the use of zolpidem tartrate extended-release tablets at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of zolpidem tartrate extended-release 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), have 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 extended-release tablets, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, zolpidem tartrate extended-release 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 extended-release tablets. Zolpidem tartrate extended-release 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 extended-release tablet 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 zolpidem tartrate extended-release tablets dosage is 6.25 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 extended-release tablets in patients with concomitant systemic illness is limited. Caution is advisable in using zolpidem tartrate extended-release 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 normals 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 an immediate-release formulation of zolpidem tartrate (10 mg) when compared to placebo. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be

taken if zolpidem tartrate extended-release tablet 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.

Zolpidem tartrate extended-release 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 an immediate-release formulation of zolpidem tartrate (10 mg) 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 zolpidem tartrate extended-release tablets 6.25 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 extended-release 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 to 17 years) with insomnia associated with ADHD given an immediate-release oral solution of zolpidem tartrate, 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:In 3-week clinical trials in adults and elderly patients (> 65 years), 3.5% (7/201) patients receiving zolpidem tartrate extended-release tablets 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.9% (2/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with zolpidem tartrate extended-release tablets was somnolence (1%).

In a 6-month study in adult patients (18 to 64 years of age), 8.5% (57/669) of patients receiving zolpidem tartrate extended-release tablets 12.5 mg as compared to 4.6% on placebo (16/349) discontinued treatment due to an adverse reaction. Reactions most commonly associated with discontinuation of zolpidem tartrate extended-release tablets included anxiety (anxiety, restlessness or agitation) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo, and depression (depression, major depression or depressed mood) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo.

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 treatment with zolpidem tartrate extended-release tablets in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of zolpidem tartrate extended-release tablets were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating zolpidem tartrate extended-release tablets 12.5 mg, the adverse reaction profile was consistent with that reported in short-term trials, except for a higher incidence of anxiety (6.3% for zolpidem tartrate extended-release tablets versus 2.6% for placebo).

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 extended-release tablets in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary 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 tables were derived from results of two placebo-controlled efficacy trials involving zolpidem tartrate extended-release tablets. These trials involved patients with primary insomnia who were treated for 3 weeks with zolpidem tartrate extended-release tablets at doses of 12.5 mg (**Table 1**) or 6.25 mg (Table 2), respectively. The tables include only adverse reactions occurring at an incidence of at least 1% for zolpidem tartrate extended-release tablets patients and with an incidence greater than that seen in the placebo patients.

Table 1. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Adults (percentage of patients reporting)

Body system/Adverse Reaction *	**Zolpidem Tartrate Extended-Release Tablet 12.5 mg (N = 102)**	**Placebo (N = 110)**
Infections and infestations		
Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
Metabolism and nutrition disorders		
Appetite disorder	1	0
Psychiatric disorders		
Hallucinations **	4	0
Disorientation	3	2
Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0

Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
Nervous system disorders		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders ***	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
Eye disorders		
Visual disturbance	3	0
Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
Ear and labyrinth disorders		
Vertigo	2	0
Tinnitus	1	0
Respiratory, thoracic and mediastinal disorders		
Throat irritation	1	0
Gastrointestinal disorders		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux disease	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0
Skin wrinkling	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0
Reproductive system and breast disorders		
Menorrhagia	1	0
General disorders and administration site		

conditions		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
Investigations		
Blood pressure increased	1	0
Body temperature increased	1	0
Injury, poisoning and procedural complications		
Contusion	1	0
Social circumstances		
Exposure to poisonous plant	1	0

*Reactions reported by at least 1% of patients treated with zolpidem tartrate extended-release tablets and at greater frequency than in the placebo group
**Hallucinations included hallucinations NOS as well as visual and hypnogogic hallucinations.
***Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Table 2. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Elderly (percentage of patients reporting)

Body System/Adverse Reaction *	**Zolpidem Tartrate Extended-Release Tablet 6.25 mg (N=99)**	**Placebo (N=106)**
Infections and infestations		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
Nervous system disorders		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders **	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		

Flatulence	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system and breast disorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

*Reactions reported by at least 1% of patients treated with zolpidem tartrate extended-release tablets and at greater frequency than in the placebo group.
**Memory disorders include: memory impairment, amnesia, anterograde amnesia.

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.

Other Adverse Reactions Observed During The Premarketing Evaluation Of Zolpidem Tartrate Extended-Release Tablet:Other treatment-emergent adverse reactions associated with participation in zolpidem tartrate extended-release tablets studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed During the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate

Immediate-release zolpidem tartrate was 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**:* Frequent: dry mouth. 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: chest pain, edema, falling, 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, drowsiness, drugged feeling, euphoria, insomnia, lethargy, lightheadedness, vertigo. Infrequent: agitation, 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: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis. 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:Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

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

Respiratory system:Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. 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.

An immediate-release formulation of 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 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 an immediate-release formulation of zolpidem tartrate (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 a single 5 mg dose of immediate-release 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 extended-release 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 Tests 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 extended-release tablets in pregnant women. Zolpidem tartrate extended-release tablets should be used during pregnancy only if the potential benefit justifies 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 extended-release tablets maximum recommended human dose (MRHD) of 12.5 mg/day (approximately 10 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 4, 20 and 100 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 4 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, 8 and 30 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 8 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 4, 20 and 100 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 4 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 extended-release tablet has 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 extended-release tablet is 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 to 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.

FDA has not required pediatric studies of zolpidem tartrate extended-release tablets in the pediatric population based on these efficacy and safety findings.

8.5 Geriatric Use

A total of 99 elderly (≥ 65 years of age) received daily doses of 6.25 mg zolpidem tartrate extended-release tablets in a 3-week placebo-controlled study. The adverse reaction profile of zolpidem tartrate extended-release tablets 6.25 mg in this population was similar to that of zolpidem tartrate extended-release tablets 12.5 mg in younger adults (≤ 64 years of age). Dizziness was reported in 8% of zolpidem tartrate extended-release tablet-treated patients compared with 3% of those treated with placebo.

The dose of zolpidem tartrate extended-release tablets in elderly patients is 6.25 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 effects were 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.

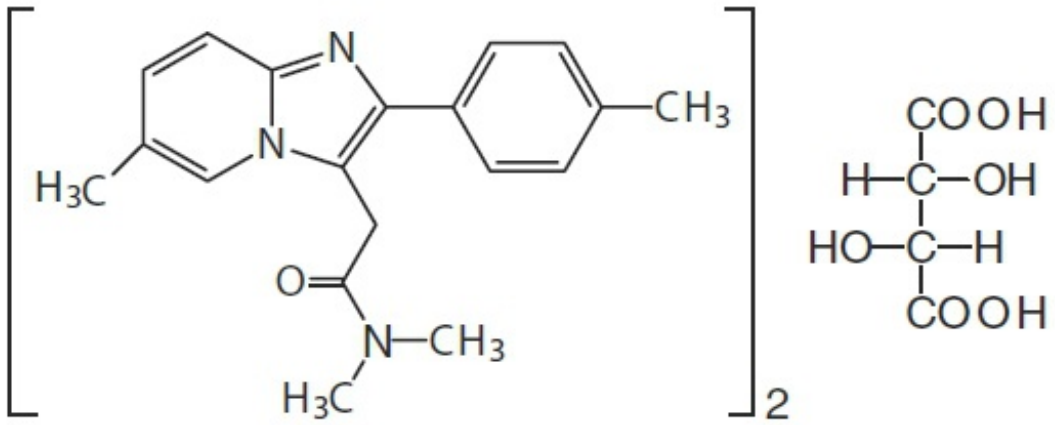
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

11 DESCRIPTION

Zolpidem tartrate extended-release tablet, USP contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Zolpidem tartrate extended-release tablet is available in 6.25 mg and 12.5 mg strengths 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.



Zolpidem tartrate extended-release tablet, USP is available for oral administration as a film-coated tablet containing 6.25 mg and 12.5 mg of zolpidem tartrate. Inactive ingredients consist of colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, red ferric oxide, talc, and titanium dioxide.

USP Dissolution test 4 used.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

12.3 Pharmacokinetics

A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of zolpidem tartrate extended-release tablet 12.5 mg and of an immediate-release formulation of zolpidem tartrate (10 mg). The terminal elimination half-life observed with zolpidem tartrate extended-release tablet (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg). The mean plasma concentration-time profiles are shown in Figure 1.

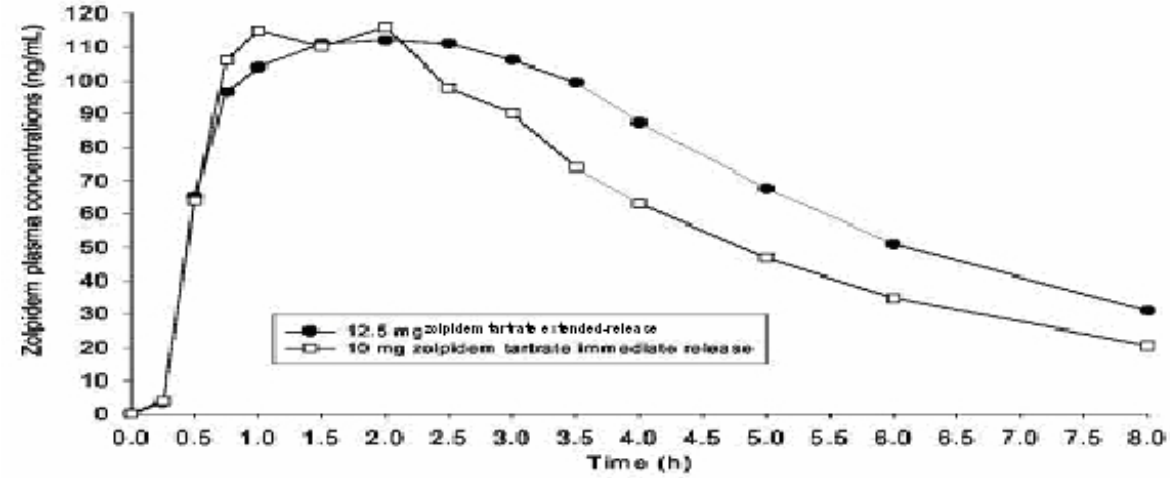


Figure 1: Mean plasma concentration-time profiles for zolpidem tartrate extended-release tablets (12.5 mg) and immediate-release zolpidem tartrate (10 mg)

In adult and elderly patients treated with zolpidem tartrate extended-release tablets, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

Absorption

Following administration of zolpidem tartrate extended-release tablets, administered as a single 12.5 mg dose in healthy male adult subjects, the mean peak concentration (C_{max}) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/ml) occurring at a median time (T_{max}) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy subjects compared the pharmacokinetics of zolpidem tartrate extended-release tablets 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 23% and 30%, respectively, while median $T_{max}$was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, zolpidem tartrate extended-release tablets should not be administered with or immediately after a meal.

Distribution

Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL.

Metabolism

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination

When zolpidem tartrate extended-release tablet was administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

Special Populations

Elderly

In 24 elderly (≥ 65 years) healthy subjects administered a single 6.25 mg dose of zolpidem tartrate extended-release tablet, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35 to 161) ng/mL occurring at a median time (T_{max}) of 2 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

Hepatic Impairment

Zolpidem tartrate extended-release tablet was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate 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

Zolpidem tartrate extended-release tablets was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation 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 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2 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, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ 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, 9, and 40 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) on mg/m^2 basis. In rats, these doses are approximately 4, 18, and 80 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 4, 20, and 100 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 20 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

14 CLINICAL STUDIES

14.1 Controlled Clinical Trials

Zolpidem tartrate extended-release tablet was evaluated in three placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

Adult outpatients (18 to 64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing zolpidem tartrate extended-release tablets 12.5 mg and placebo. Zolpidem tartrate extended-release tablets 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Zolpidem tartrate extended-release tablet 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment. Zolpidem tartrate extended-release tablet 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

Elderly outpatients (≥ 65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing zolpidem tartrate extended-release tablet 6.25 mg and placebo. Zolpidem tartrate extended-release tablets 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Zolpidem tartrate extended-release tablet 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment. Zolpidem tartrate extended-release tablets 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, in patients treated with zolpidem tartrate extended-release tablets, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

In a 24-week double-blind, placebo controlled, randomized study in adult outpatients (18 to 64 years) with primary insomnia (N=1025), zolpidem tartrate extended-release tablet 12.5 mg administered as needed (3 to 7 nights per week) was superior to placebo over 24 weeks, on patient global impression regarding aid to sleep, and on patient-reported specific sleep parameters for sleep induction and sleep maintenance with no significant increased frequency of drug intake observed over time.

14.2 Studies Pertinent To Safety Concerns For Sedative/Hypnotic Drugs

Next-Day Residual Effects

In five clinical studies [three controlled studies in adults (18 to 64 years of age) administered zolpidem tartrate extended-release tablets 12.5 mg and two controlled studies in the elderly (≥ 65 years of age) administered zolpidem tartrate extended-release tablets 6.25 mg or 12.5 mg], the effect of zolpidem tartrate extended-release tablets on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with zolpidem tartrate extended-release tablets 12.5 mg and 6.25 mg using self-ratings of sedation.

During the 3-week studies, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg zolpidem tartrate extended-release tablets versus 2% of the placebo group; next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg zolpidem tartrate extended-release tablets versus 5% of the placebo group *[see* **ADVERSE REACTIONS (6)***]*. In a 6-month study, the overall incidence of next-day somnolence was 5.7% in the zolpidem tartrate extended-release tablet group as compared to 2% in the placebo group.

Rebound Effects

Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment,

is observed with short- and intermediate-acting hypnotics. In the two 3-week placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of zolpidem tartrate extended-release tablets. On the second night, there was no worsening compared to baseline in the zolpidem tartrate extended-release tablets group.

In a 6-month placebo-controlled study in which zolpidem tartrate extended-release tablet was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Zolpidem tartrate extended-release tablets, USP are available as follows:

6.25 mg, dark pink, round, biconvex film-coated tablets debossed with SZ on one side and 228 on the other side.

NDC 0781-5315-31, bottles of 30 tablets

NDC 0781-5315-01, bottles of 100 tablets

NDC 0781-5315-05, bottles of 500 tablets

12.5 mg, light pink, round, biconvex film-coated tablets debossed with SZ on one side and 229 on the other side.

NDC 0781-5316-31, bottles of 30 tablets

NDC 0781-5316-01, bottles of 100 tablets

NDC 0781-5316-05, bottles of 500 tablets

The tablets are to be swallowed whole and should not be crushed, chewed, or divided.

Storage

Store at 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant, child-resistant container.

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 extended-release tablet is 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 extended-release tablets should not be crushed, divided, or chewed, and should not be taken with or immediately after a meal. Advise patients NOT to take zolpidem tartrate extended-release tablets when drinking alcohol.

17.4 Medication Guide

MEDICATION GUIDE

Zolpidem Tartrate Extended-Release Tablets, USP

Read the Medication Guide that comes with zolpidem tartrate extended release 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 extended-release tablet?

After taking zolpidem tartrate extended-release 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 extended-release 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 extended-release tablets.

Important:

1. Take zolpidem tartrate extended-release tablets exactly as prescribed

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

2. Do not take zolpidem tartrate extended-release 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 extended-release tablet with your other medicines.
- cannot get a full night's sleep

What is zolpidem tartrate extended-release tablet?

Zolpidem tartrate extended-release tablet is a sedative-hypnotic (sleep) medicine. Zolpidem tartrate extended-release tablet is used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep
- waking up often during the night

Zolpidem tartrate extended-release tablet is not for children.

Zolpidem tartrate extended-release tablet is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep zolpidem tartrate extended-release tablets in a safe place to prevent misuse and abuse. Selling or giving away zolpidem tartrate extended-release 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 extended-release tablets?

Do not take zolpidem tartrate extended-release 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 extended-release tablets.

Zolpidem tartrate extended-release tablets may not be right for you. Before starting zolpidem tartrate extended-release 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 extended-release 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 extended-release tablets?

- Take zolpidem tartrate extended-release tablets exactly as prescribed. Do not take more zolpidem tartrate extended-release tablets than prescribed for you.
- **Take zolpidem tartrate extended-release tablets right before you get into bed.**
- **Do not take zolpidem tartrate extended-release tablets unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**
- Swallow zolpidem tartrate extended-release tablets whole. Do not chew or break the tablets. Tell your doctor if you cannot swallow tablets whole.

- For faster sleep onset, zolpidem tartrate extended-release 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 problems.
- If you take too much zolpidem tartrate extended-release 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 extended-release tablets?

Serious side effects of zolpidem tartrate extended-release 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 extended-release tablet?)
- **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 extended-release 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 extended-release tablets.

The most common side effects of zolpidem tartrate extended-release tablets are:

- headache
- sleepiness
- dizziness
- You may still feel drowsy the next day after taking zolpidem tartrate extended-release tablets. **Do not drive or do other dangerous activities after taking zolpidem tartrate extended-release 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 extended-release tablets. Ask your doctor or pharmacist for more information.

How should I store zolpidem tartrate extended-release tablets?

- Store at 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature].
- **Keep zolpidem tartrate extended-release tablets and all medicines out of reach of children.**

General Information about zolpidem tartrate extended-release tablets

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use zolpidem tartrate extended-release tablets for a condition for which it was not prescribed.
- Do not share zolpidem tartrate extended-release 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 extended-release tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about zolpidem tartrate extended-release tablets that is written for healthcare professionals. For more information about zolpidem tartrate extended-release tablets, call Sandoz Inc. at 1-800-525-8747

What are the ingredients in zolpidem tartrate extended-release tablets?

Active Ingredient: Zolpidem tartrate

Inactive Ingredients: colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, red ferric oxide, talc, and titanium dioxide.

Call your doctor for medical advice about side effects. You may report side effects to Sandoz Inc. at 1-800-525-8747 or to FDA at 1-800-FDA-1088

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

Manufactured in Slovenia by Lek Pharmaceuticals d.d.

for Sandoz Inc., Princeton, NJ 08540

Rev. February 2012

Zolpidem ER 12.5mg (CIV) Tablet

ZOLPIDEM TARTRATE

zolpidem tartrate tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:63629-4597(NDC:0781-5316)
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

ZOLPIDEM TARTRATE (ZOLPIDEM)	ZOLPIDEM TARTRATE	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
HYDROXYPROPYL CELLULOSE	
HYPROMELLOSES	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
POLYETHYLENE GLYCOLS	
FERRIC OXIDE RED	
TALC	
TITANIUM DIOXIDE	

Product Characteristics

Color	PINK (Light Pink)	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	SZ;229
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4597-1	30 in 1 BOTTLE		
2	NDC:63629-4597-2	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090107	10/31/2011	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-4597), RELABEL(63629-4597)