HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOLPIDEM TARTRATE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for ZOLPIDEM TARTRATE EXTENDED-RELEASE TABLETS.

ZOLPIDEM tartrate extended-release tablets, USP, for oral use CIV

Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Dosage and Administration, Dosage in Adults **(2.1)** 8/2016

Warnings and Precautions, CNS Depressant Effects and Next Day Impairment **(5.1)** 8/2016

INDICATIONS AND USAGE

Zolpidem tartrate extended-release tablets, a gamma-aminobutyric acid (GABA) A agonist are indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. **(1)**

DOSAGE AND ADMINISTRATION

- Use the lowest dose effective for the patient and must not exceed a total of 12.5 mg daily **(2.1)**
- Recommended initial dose is a single dose of 6.25 mg for women, and a single dose of 6.25 or 12.5 mg for men, immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening **(2.1)**
- Geriatric patients and patients with hepatic impairment: Recommended dose is 6.25 mg for men and women **(2.2)**
- Lower doses of CNS depressants may be necessary when taken concomitantly with zolpidem tartrate extended-release tablets **(2.3)**
- Tablets to be swallowed whole, not to be crushed, divided or chewed **(2.4)**
- The effect of zolpidem tartrate extended-release tablets may be slowed if taken with or immediately after a meal **(2.4)**

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Known hypersensitivity to zolpidem **(4)**

WARNINGS AND PRECAUTIONS

- CNS depressant effects: Impaired alertness and motor coordination, including risk of morning impairment. Caution patients against driving and other activities requiring complete mental alertness the morning after use. **(5.1)**
- Need to evaluate for co-morbid diagnoses: Revaluate if insomnia persists after 7 to 10 days of use **(5.2)**
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. **(5.3)**
- "Sleep-driving" and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. **(5.4)**
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. **(5.5)**
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function **(5.6)**
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation **(5.7, 9.3)**
- Severe Injuries: Drowsiness may lead to fall including severe injuries **(5.8)**

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 Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

DRUG INTERACTIONS

- CNS depressants: including alcohol: Possible adverse additive CNS-depressant effects **(5.1, 7.1)**
- Imipramine: Decreased alertness observed **(7.1)**
- Chlorpromazine: Impaired alertness and psychomotor performance observed **(7.1)**
- CYP3A4 inducers (e.g. rifampin): Combination use may decrease effect **(7.2)**
- CYP3A4 inhibitors (e.g. ketoconazole): Combination use may increase effect **(7.2)**

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2016

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 Tablets, USP, are 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

2.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken only once per night immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next day impairment of driving and other activities that require full alertness *[see* **Warnings and Precautions (5.1)***]*. The total dose of zolpidem tartrate extended-release tablets should not exceed 12.5 mg once daily immediately before bedtime. Zolpidem tartrate extended-release tablets should be taken as a single dose and should not be readministered during the same night.

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

2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of zolpidem tartrate extended-release tablets in both of these patient populations is 6.25 mg once daily immediately before bedtime *[see* **Warnings and Precautions (5.1); Use in Specific Populations (8.5)***]*.

2.3 Use with CNS Depressants

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

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 are available as extended-release tablets 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 yellow round film coated tablets engraved with "A117" on one side and plain on the other side.

Zolpidem Tartrate Extended-Release Tablets, 12.5 mg are white to off-white round film coated tablets engraved with "A116" on one side and plain on the other side.

4 CONTRAINDICATIONS

Zolpidem tartrate extended-release tablets are contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions include anaphylaxis and angioedema *[see* **Warnings and Precautions (5.3)***]*.

5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-Day Impairment

Zolpidem tartrate extended-release tablets are a central nervous system (CNS) depressant and can impair daytime function in some patients even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e. less than formal psychomotor testing). While pharmacodynamic tolerance or adaptation to some adverse depressant effects of zolpidem tartrate extended-release tablets may develop, patients using zolpidem tartrate extended-release tablets should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.

Additive effects occur with concomitant use of other CNS depressants (e.g. benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use. Downward dose adjustment of zolpidem tartrate extended-release tablets and concomitant CNS depressants should be considered *[see* **Dosage and Administration (2.3)***]*.

The use of zolpidem tartrate extended-release tablets with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if zolpidem tartrate extended-release tablets is taken with less than a full night of sleep remaining (7 to 8 hours); if higher than the recommended dose is taken; if coadministered with other CNS depressants or alcohol; or coadministered with other drugs that increase the blood levels of zolpidem. Patients should be warned against driving and other activities requiring complete mental alertness if zolpidem tartrate extended-release tablets is taken in these circumstances *[see* **DOSAGE AND ADMINISTRATION (2)** *and* **Clinical Studies (14.2)***]*.

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, reduced alertness and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7 to 8 hours) is recommended.

5.2 Need to Evaluate for Co-morbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or 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.

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.4 Abnormal Thinking and Behavioral Changes

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

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

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" have occurred with zolpidem tartrate extended-release tablets alone at therapeutic doses, the coadministration of alcohol and other CNS depressants increases 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 also occur.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.5 Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

5.6 Respiratory Depression

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

5.7 Withdrawal Effects

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

5.8 Severe Injuries

Zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries. Severe injuries such as hip fractures and intracranial hemorrhage have been reported.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

Associated with discontinuation of treatment: 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 were 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 Tablets 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 Tablets 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 tablets:

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, 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, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

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

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

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

7 DRUG INTERACTIONS

7.1 CNS-active Drugs

Coadministration of zolpidem with other CNS depressants increases the risk of CNS depression. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability *[see* **Warnings and Precautions (5.1)***]*. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

Imipramine, Chlorpromazine

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 *[see* **Clinical Pharmacology (12.3)***]*.

Haloperidol

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration *[see* **Clinical Pharmacology (12.3)***]*.

Alcohol

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

Sertraline Concomitant administration of zolpidem and sertraline increases exposure to zolpidem *[see* **Clinical Pharmacology (12.3)***]*.

Fluoxetine

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance *[see* **Clinical Pharmacology (12.3)***]*.

7.2 Drugs that Affect Drug Metabolism via Cytochrome P450

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

CYP3A4 Inducers

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of CYP3A4 inducers in combination with zolpidem may decrease the efficacy of zolpidem *[see* **Clinical Pharmacology (12.3)***]*.

CYP3A4 Inhibitors

Ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to and pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when a CYP3A4 inhibitor and zolpidem are given together *[see* **Clinical Pharmacology (12.3)***]*.

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. Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. Zolpidem tartrate extended-release 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 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/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 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/day, 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/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m^2 basis.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

Zolpidem is excreted in human milk. Caution should be exercised when zolpidem tartrate extended-release tablets are administered to a nursing woman.

8.4 Pediatric Use

Zolpidem tartrate extended-release tablets are not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

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

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 tablets-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 (5.1)***]*.

8.6 Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men. C_{max} and AUC parameters of zolpidem from zolpidem tartrate extended-release tablets were, respectively, approximately 50% and 75% higher at the same dose in adult female subjects compared to adult male subjects. Between 6 and 12 hours after dosing, zolpidem concentrations were 2- to 3 fold higher in adult female compared to adult male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of zolpidem tartrate

PHARMACIST — DETACH HERE

MEDICATION GUIDE

Zolpidem Tartrate (zole-PI-dem TAR-trate) Extended-Release Tablets, USP CIV

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 healthcare provider about your medical condition or treatment.

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

- **Do not take more zolpidem tartrate extended-release tablets than prescribed.**
- **Do not take zolpidem tartrate extended-release tablets unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take zolpidem tartrate extended-release tablets right before you get in bed, not sooner.**

Zolpidem tartrate extended-release tablets may cause serious side effects that you may not know are happening to you. These side effects include:

- sleepiness during the day
- not thinking clearly
- act strangely, confused, or upset
- "sleep-walking" or doing other activities when you are asleep like:
  - eating
  - talking
  - having sex
  - driving a car

Call your healthcare provider right away if you find out that you have done any of the above activities after taking zolpidem tartrate extended-release tablets.

You should not drive a car or do things that require clear thinking the day after you take zolpidem tartrate extended-release tablets.

Do not take zolpidem tartrate extended-release tablets if you:

- drank alcohol that evening or before bed
- take other medicines that can make you sleepy. Taking zolpidem tartrate extended-release tablets with other drugs can cause side effects. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take zolpidem tartrate extended-release tablets with your other medicines.
- cannot get a full night's sleep

What is zolpidem tartrate extended-release tablets?

Zolpidem tartrate extended-release tablets are a sedative-hypnotic (sleep) medicine. Zolpidem tartrate extended-release tablets are 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

It is not known if zolpidem tartrate extended-release tablets are safe and effective in children under the age of 18 years.

Zolpidem tartrate extended-release tablets are 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 healthcare provider 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 zolpidem or any other ingredients in zolpidem tartrate extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in zolpidem tartrate extended-release tablets.
- Do not take zolpidem tartrate extended-release tablets if you have had an allergic reaction to drugs containing zolpidem, such as zolpidem tartrate, Edluar, Zolpimist, or Intermezzo.

Symptoms of a serious allergic reaction to zolpidem can include:

- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

What should I tell my healthcare provider before taking 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 healthcare provider about all of your health conditions, including if you:

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

Tell your healthcare provider 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 unless your healthcare provider tells you to.**

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

How should I take zolpidem tartrate extended-release tablets?

- See **"What is the most important information I should know about zolpidem tartrate extended-release tablets?"**

- Take zolpidem tartrate extended-release tablets exactly as prescribed. Only take 1 zolpidem tartrate extended-release tablets a night if needed.
- Do not take zolpidem tartrate extended-release tablets if you drank alcohol that evening or before bed.
- You should not take zolpidem tartrate extended-release tablets with or right after a meal. Zolpidem tartrate extended-release tablets may help you fall asleep faster if you take it on an empty stomach.
- Take zolpidem tartrate extended-release tablets whole. Do not break, crush, dissolve or chew zolpidem tartrate extended-release tablets before swallowing. If you cannot swallow zolpidem tartrate extended-release tablets whole, tell your healthcare provider. You may need a different medicine.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much zolpidem tartrate extended-release tablets or overdose, get emergency treatment.

What are the possible side effects of zolpidem tartrate extended-release tablets?

Zolpidem tartrate extended-release tablets may cause serious side effects including:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See "**What is the most important information I should know about zolpidem tartrate extended-release 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 extended-release tablets.
- **falls, which may lead to severe injuries**

Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using zolpidem tartrate extended-release tablets.

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

- headache
- sleepiness
- dizziness
- drowsiness the next day after you take zolpidem tartrate extended-release tablets

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
- stomach area pain

These are not all the side effects of zolpidem tartrate extended-release tablets. Ask your healthcare provider or pharmacist for more information.

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

How should I store zolpidem tartrate extended-release tablets?

Store zolpidem tartrate extended-release tablets at 20°C to 25°C (68°F to 77°F).

Keep zolpidem tartrate extended-release tablets and all medicines out of reach of children.

General Information about the safe and effective use of 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 healthcare provider. You can ask your healthcare provider or pharmacist for information about zolpidem tartrate extended-release tablets that is written for healthcare professionals. **To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

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

Active Ingredient: Zolpidem tartrate

Inactive Ingredients:

The 6.25 mg tablets contain: colloidal silicon dioxide, D&C yellow #10 aluminum lake, FD&C yellow #6/sunset yellow FCF aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, sugar, titanium dioxide and talc.

The 12.5 mg tablets contain: colloidal silicon dioxide, hypromellose, magnesium stearate, polydextrose, polyethylene glycol, sugar, titanium dioxide and triacetin.

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

Manufactured by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R08/16 OS117A-01-50-08

extended-release tablets for adult women is 6.25 mg, and the recommended dose for adult men is 6.25 or 12.5 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of zolpidem tartrate extended-release tablets in geriatric patients is 6.25 mg regardless of gender.

9 DRUG ABUSE AND DEPENDENCE

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

9.2 Abuse
Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

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

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg 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. Post-marketing 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.

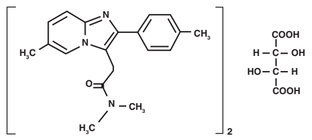
10.2 Recommended Treatment
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, 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 Tablets, USP, contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A agonist of the imidazopyridine class. Zolpidem tartrate extended-release tablets are available in 6.25 mg and 12.5 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. Zolpidem tartrate extended-release tablets are film coated containing a hydrogel-matrix core that provides extended-release of the drug content.

The 6.25 mg zolpidem tartrate extended-release tablets contain the following inactive ingredients: colloidal silicon dioxide, D&C yellow #10 aluminum lake, FD&C yellow #6/sunset yellow FCF aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, sugar, titanium dioxide and talc. The 12.5 mg zolpidem tartrate extended-release tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, polydextrose, polyethylene glycol, sugar, titanium dioxide and triacetin.

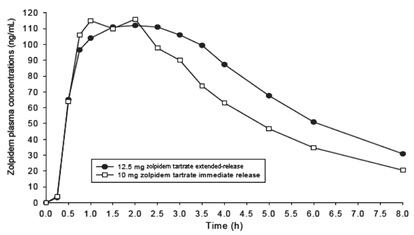
Meets USP Dissolution Test 3.

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 bind to 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 tablets 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 tablets (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 tablets were 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 tablets, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (T_{max}) of 2.0 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 tablets were 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)***]*.

Renal Impairment:
Zolpidem tartrate extended-release tablets were 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 ClCr = 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. 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.

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

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

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

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

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

Drugs that Affect Drug Metabolism via Cytochrome P450
Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

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

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (-73%), C_{max} (-58%), and $T_{1/2}$ (-36 %) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem *[see* **Drug Interaction (7.2)***]*.

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30 %) along with an increase in the pharmacodynamic effects of zolpidem *[see* **Drug Interaction (7.2)***]*.

Additionally, fluvoxamine (a strong inhibitor of CYP1A2 and a weak inhibitor of CYP3A4 and CYP2C9) and ciprofloxacin (a strong inhibitor of CYP1A2) and a moderate inhibitor of CYP3A4) are also likely to inhibit zolpidem's metabolic pathways, potentially leading to an increase in zolpidem exposure.

Other Drugs with No Interactions with Zolpidem
A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg. 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/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 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 tablets were 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 tablets 12.5 mg were also 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 tablets 12.5 mg were 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 tablets 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 tablets 6.25 mg were 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 were 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 tablets 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 tablets 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 tablets were 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, 6.25 mg are available as yellow round film coated tablets engraved with "A117" on one side and plain on the other side. They are supplied as follows:

NDC Number Size
10370-117-10 bottle of 100

Zolpidem Tartrate Extended-Release Tablets, USP, 12.5 mg are available as white to off-white round film coated tablets engraved with "A116" on one side and plain on the other side. They are supplied as follows:

NDC Number Size
10370-116-10 bottle of 100

***Store at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature].**

17 PATIENT COUNSELING INFORMATION

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

CNS Depressant Effects and Next-Day Impairment
Tell patients that zolpidem tartrate extended-release tablets can cause next-day impairment even when used as prescribed, and that this risk is increased if dosing instructions are not carefully followed. Caution patients against driving and other activities requiring complete mental alertness the day after use. Inform patients that impairment can be present despite feeling fully awake.

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

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

Suicide
Tell patients to immediately report any suicidal thoughts.

Alcohol and Other Drugs
Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use zolpidem tartrate extended-release tablets if they drank alcohol that evening or before bed.

Tolerance, Abuse, and Dependence
Tell patients not to increase the dose of zolpidem tartrate extended-release tablets on their own, and to inform you if they believe the drug "does not work".

Administration Instructions
Patients should be counseled to take zolpidem tartrate extended-release tablets right before they get into bed and only when they are able to stay in bed a full night (7 to 8 hours) before being active again. Zolpidem tartrate extended-release tablets should not be taken with or immediately after a meal. Advise patients NOT to take zolpidem tartrate extended-release tablets if they drank alcohol that evening.

MEDICATION GUIDE

Zolpidem Tartrate
(zole-PI-dem TAR-trate)
Extended-Release Tablets, USP
C-IV

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 healthcare provider about your medical condition or treatment.

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

- **Do not take more zolpidem tartrate extended-release tablets than prescribed.**
- **Do not take zolpidem tartrate extended-release tablets unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take zolpidem tartrate extended-release tablets right before you get in bed, not sooner.**

Zolpidem tartrate extended-release tablets may cause serious side effects that you may not know are happening to you. These side effects include:

- sleepiness during the day
- not thinking clearly
- act strangely, confused, or upset
- "sleep-walking" or doing other activities when you are asleep like:
  - eating
  - talking
  - having sex
  - driving a car

Call your healthcare provider right away if you find out that you have done any of the above activities after taking zolpidem tartrate extended-release tablets.

You should not drive a car or do things that require clear thinking the day after you take zolpidem tartrate extended-release tablets.

Do not take zolpidem tartrate extended-release tablets if you:

- drank alcohol that evening or before bed
- take other medicines that can make you sleepy. Taking zolpidem tartrate extended-release tablets with other drugs can cause side effects. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take zolpidem tartrate extended-release tablets with your other medicines.
- cannot get a full night's sleep

What is zolpidem tartrate extended-release tablets?
Zolpidem tartrate extended-release tablets are a sedative-hypnotic (sleep) medicine. Zolpidem tartrate extended-release tablets are 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

It is not known if zolpidem tartrate extended-release tablets are safe and effective in children under the age of 18 years.

Zolpidem tartrate extended-release tablets are 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 healthcare provider 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 zolpidem or any other ingredients in zolpidem tartrate extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in zolpidem tartrate extended-release tablets.
- Do not take zolpidem tartrate extended-release tablets if you have had an allergic reaction to drugs containing zolpidem, such as zolpidem tartrate, Ediuar, Zolpimist, or Intermezzo.

Symptoms of a serious allergic reaction to zolpidem can include:

- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

What should I tell my healthcare provider before taking 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 healthcare provider about all of your health conditions, including if you:

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

Tell your healthcare provider 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 unless your healthcare provider tells you to.**

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

How should I take zolpidem tartrate extended-release tablets?

- See "**What is the most important information I should know about zolpidem tartrate extended-release tablets?**"
- Take zolpidem tartrate extended-release tablets exactly as prescribed. Only take 1 zolpidem tartrate extended-release tablets a night if needed.
- Do not take zolpidem tartrate extended-release tablets if you drank alcohol that evening or before bed.
- You should not take zolpidem tartrate extended-release tablets with or right after a meal. Zolpidem tartrate extended-release tablets may help you fall asleep faster if you take it on an empty stomach.
- Take zolpidem tartrate extended-release tablets whole. Do not break, crush, dissolve or chew zolpidem tartrate extended-release tablets before swallowing. If you cannot swallow zolpidem tartrate extended-release tablets whole, tell your healthcare provider. You may need a different medicine.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much zolpidem tartrate extended-release tablets or overdose, get emergency treatment.

What are the possible side effects of zolpidem tartrate extended-release tablets?

Zolpidem tartrate extended-release tablets may cause serious side effects including:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See "**What is the most important information I should know about zolpidem tartrate extended-release 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 extended-release tablets.
- **falls, which may lead to severe injuries**

Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using zolpidem tartrate extended-release tablets.

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

- headache
- sleepiness
- dizziness
- drowsiness the next day after you take zolpidem tartrate extended-release tablets

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
- stomach area pain

These are not all the side effects of zolpidem tartrate extended-release tablets. Ask your healthcare provider or pharmacist for more information.

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

How should I store zolpidem tartrate extended-release tablets?
Store zolpidem tartrate extended-release tablets at 20°C to 25°C (68°F to 77°F).

Keep zolpidem tartrate extended-release tablets and all medicines out of reach of children.

General Information about the safe and effective use of 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 healthcare provider. You can ask your healthcare provider or pharmacist for information about zolpidem tartrate extended-release tablets that is written for healthcare professionals. **To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

What are the ingredients in zolpidem tartrate extended-release tablets?
Active Ingredient: Zolpidem tartrate

Inactive Ingredients:
The 6.25 mg tablets contain: colloidal silicon dioxide, D&C yellow #10 aluminum lake, FD&C yellow #6/sunset yellow FCF aluminum lake, hypromellose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, sugar, titanium dioxide and talc.

The 12.5 mg tablets contain: colloidal silicon dioxide, hypromellose, magnesium stearate, polydextrose, polyethylene glycol, sugar, titanium dioxide and triacetin.

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

Manufactured by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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