ZOLPIDEM TARTRATE

ZOLDEM®

10 mg FILM-COATED TABLET

SEDATIVE / HYPNOTIC

FORMULATION
Each film-coated tablet contains:
Zolpidem tartrate .....10 mg

PRODUCT DESCRIPTION
Zolpidem tartrate (Zoldem) is a light blue, capsule-shaped, film-coated tablet, bisected on one side and plain on the other side.

PHARMACOLOGY
Zolpidem is a nonbenzodiazepine sedative-hypnotic which preferentially binds to omega-1 receptor subtype (benzodiazepine-1 or BZ_1) which corresponds to the gamma aminobutyric acid $(GABA)_A$ receptor containing the α_1-subunit. In contrast, benzodiazepines nonselectively bind to both omega-1 and omega-2 subtypes. The modulation of the chloride anion channel via this $GABA_A$ receptor leads to the specific sedative effects of zolpidem.
In humans, zolpidem decreases sleep latency and the number of awakenings, and increases sleep duration and sleep quality**.** These effects are associated with a characteristic electroencephalogram (EEG) profile, different from that of the benzodiazepines. In studies that measured the percentage of time spent in each sleep stage, zolpidem has generally been shown to preserve sleep stages. At the recommended dose, zolpidem has no influence on the paradoxical sleep duration (rapid eye movement or REM). The preservation of deep sleep (stages 3 and 4 slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem.
The selectivity of zolpidem for BZ_1 receptors is thought to be responsible for its greater potency as a sedative-hypnotic as opposed to an anticonvulsant muscle relaxant agent. The properties of zolpidem can be summarized as: sedative>anticonvulsant>muscle relaxant. This contrasts with those of benzodiazepines, which can be represented as anticonvulsant>muscle relaxant>sedative.

PHARMACOKINETICS
Zolpidem tartrate bioavailability is about 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range of 5 to 20 mg. The peak plasma concentration (C_{max}) is reached at 0.5 to 3 hours.
A food effect study showed that with food, mean area under the curve (AUC) and C_{max} were decreased by 15% and 25%, respectively, while mean time to reach plasma concentration (T_{max}) was prolonged by 60% (from 1.4 to 2.2 hours). The half-life remained unchanged. This study showed that for faster sleep onset, zolpidem should not be given with or immediately after a meal.
Total protein binding was found to be 92.5±0.1% and remained constant; independent of concentration between 40 and 790 ng/mL. The volume of distribution is 0.54 ± 0.02 L/kg. Zolpidem tartrate did not accumulate in young adults following nightly dosing of 20 mg tablets for two weeks.
Zolpidem tartrate is metabolized in the liver via oxidation and hydroxylation, principally by CYP3A4 and to a lesser extent by CYP1A2 and CYP2D6. It has no active metabolites. A moderate amount of the drug is subject to first-pass metabolism (~30%).
Zolpidem tartrate plasma elimination half-life ($t_{1/2}$) is approximately 2.4 hours and with duration of action of up to six hours. Zolpidem tartrate is eliminated entirely by hepatic metabolism to inactive metabolites, mainly in the urine (56%) and in the feces (37%). It does not have an inducer effect on hepatic enzymes.

Special Population:
Elderly: Zolpidem tartrate mean C_{max}, $t_{1/2}$, and AUC were significantly increased in the elderly compared to young adults. Zolpidem tartrate did not accumulate in elderly subjects following nightly oral dosing of 10 mg for one week.
Hepatic Impairment: After a single 20 mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng.hr/mL) higher, respectively, in hepatically-compromised patients. T_{max} did not change. The mean $t_{1/2}$ in cirrhotic patients of 9.9 hours was greater than that observed in normal subjects of 2.2 hours. Dosing should be adjusted in patients with hepatic insufficiency**.**
Renal Impairment: No statistically significant differences were observed for C_{max}, T_{max}, $t_{1/2}$, and AUC between the first and last of drug administration when baseline concentration adjustments were made. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem tartrate pharmacokinetics were not significantly different in renally impaired patients. Dosage adjustment is not recommended.
Gender: Women clear zolpidem tartrate from the body at a lower rate than men. C_{max} and AUC parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. In geriatric patients, clearance of zolpidem tartrate is similar in men and women.

INDICATION
For the short-term treatment of insomnia characterized by difficulties with sleep initiation.

DOSAGE AND ADMINISTRATION
Zolpidem tartrate must be initiated with the lowest recommended dose and used for the shortest possible time.
Zolpidem tartrate acts rapidly and therefore should be taken immediately before bedtime.
Zolpidem tartrate should be administered without food. The effect of the drug may be slowed by ingestion with or immediately after a meal.
The dose of zolpidem tartrate should be individualized.

Recommended Zolpidem Adult Oral Dose:
Adults below 65 years old: Initially, 5 mg (women) and either 5 or 10 mg (men), taken only once per day immediately before bedtime with at least 7 to 8 hours remaining before the planned time of awakening.
If the 5 mg dose is not effective, the dose can be increased to 10 mg.
In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness.
The recommended initial doses for women and men are different because zolpidem tartrate clearance is lower in women.
Maximum dose: 10 mg once per day immediately before bedtime.
The duration of treatment should usually vary from few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.
As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks. Extending treatment should only be done after careful reevaluation of the patient.

Special Population:
Elderly or debilitated patients:
5 mg once per day immediately before bedtime these patients may be especially sensitive to the effects of zolpidem tartrate, thus the recommended dose should not be exceeded.

Patients with hepatic insufficiency: As clearance and metabolism of zolpidem tartrate is reduced in hepatic impairment, dosage should begin at 5 mg once per day immediately before bedtime in these patients with particular caution being exercised in elderly patients.
In adults (under 65 years old), dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated.
Or, as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to zolpidem or to other ingredients in the formulation
- Obstructive sleep apnea
- Myasthenia gravis
- Severe hepatic insufficiency
- Acute and/or severe respiratory depression
- History of abuse of drugs, alcohol, or other substances
- Children

WARNINGS AND PRECAUTIONS
CNS depressant effects and next day impairment
Zolpidem tartrate, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Coadministration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustment of zolpidem tartrate and of other concomitant CNS depressants may be necessary when zolpidem tartrate is administered with such agents because of the potentially additive effects. The use of zolpidem tartrate with other sedative-hypnotics (including other zolpidem products) at bedtime or in the middle of the night is not recommended.

The risk of next-day psychomotor impairment, including impaired driving, is increased if zolpidem tartrate is taken with less than a full night of sleep remaining (7 to 8 hours); if a higher than the recommended dose is taken; if coadministered with other CNS depressants; or if coadministered with other drugs that increase the blood levels of zolpidem tartrate. Patients should be cautioned against driving and other activities requiring complete mental alertness if zolpidem tartrate is taken in these circumstances.

Abnormal thinking and behavioral changes
Abnormal thinking and behavior changes have been reported in patients treated with sedative/hypnotics, including zolpidem tartrate. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.
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-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" have occurred with zolpidem tartrate alone at therapeutic doses, the concomitant use of zolpidem tartrate with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of zolpidem tartrate at doses exceeding the maximum recommended dose. Discontinuation of zolpidem tartrate should be strongly considered for patients who report a "sleep-driving" episode due to the risk to the patient and the community**.**
Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuropsychiatric symptoms may also occur**.**
It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. However, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Evaluation for co-morbid diagnoses
Symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder**.** 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**.** These findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem tartrate.

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

Respiratory depression
Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if zolpidem tartrate is prescribed to patients with compromised respiratory function. There have been postmarketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment. The risk of respiratory depression should be considered prior to prescribing zolpidem tartrate in patients with respiratory impairment including sleep apnea and myasthenia gravis.

Severe anaphylactic and anaphylactoid reactions
Rare cases of angioedema involving the tongue, glottis or larynx have been observed in patients after the first or subsequent doses of sedative-hypnotics, including zolpidem tartrate. Additional symptoms are dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Airway obstruction may occur and may be fatal if angioedema involves the throat, glottis or larynx. If patient develops angioedema, discontinue zolpidem tartrate and do not attempt to reinitiate treatment.

Tolerance
Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks.

Drug Abuse and Dependence
Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Patients with history of addiction to or abuse of drugs or alcohol and/or concomitant psychiatric illness are at increased risk for misuse, abuse and addiction of zolpidem tartrate. Therefore, these patients should be closely monitored during zolpidem tartrate therapy**.**
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.

Amnesia
Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. This condition occurs most often several hours after ingesting the product; therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours.

Psychiatric and "paradoxical" reactions
Reactions such as restlessness, aggravated insomnia, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral effects are known to occur when using benzodiazepines or benzodiazepine-like agents. Should this occur, zolpidem tartrate should be discontinued. These reactions are more likely to occur in the elderly**.**

Rebound insomnia
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions such as mood changes, anxiety and restlessness.
Patient should be informed of the possibility of rebound phenomena, thus minimizing anxiety over such symptoms should they occur when the drug is discontinued. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate.
There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can manifest within the dosage interval, particularly when the dosage is high.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Alcohol:** Concomitant use with zolpidem tartrate is not recommended. The sedative effect may be enhanced when zolpidem tartrate is used in combination with alcohol. This affects the ability to drive or use machines.
- **Imipramine:** Concomitant use of imipramine and zolpidem tartrate produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine; however, there was an additive effect of decreased alertness.
- **Chlorpromazine:** Concomitant use of chlorpromazine and zolpidem tartrate produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.
- **Fluoxetine:** After multiple doses of zolpidem tartrate and fluoxetine, an increase in the zolpidem tartrate half-life (17%) was observed. There was no evidence of an addictive effect in psychomotor performance.
- **Sertraline:** Concomitant use of zolpidem tartrate and sertraline increases exposure to zolpidem tartrate. After five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg, zolpidem tartrate C_{max} was significantly higher (43%) and T_{max} was significantly decreased (-53%) This interaction may cause increased drowsiness. Also, isolated cases of visual hallucinations were reported.
- **Rifampicin:** Zolpidem tartrate plasma concentrations and effects are significantly reduced by rifampicin.
- **Ketoconazole:** Increased pharmacodynamic effects of zolpidem tartrate.
  Consideration should be given to using lower dose of zolpidem tartrate when ketoconazole and zolpidem tartrate are given together**.**
  Patients should be advised that the use of zolpidem tartrate with ketoconazole may enhance the sedative effects.
- **Itraconazole:** Concomitant use resulted in 34% increase in AUC_{∞} of zolpidem. There were no significant pharmacodynamic effects of zolpidem tartrate on subjective drowsiness, postural sway, or psychomotor performance.
- **Haloperidol:** Concomitant use showed no effect of haloperidol on the pharmacokinetics and pharmacodynamics of zolpidem tartrate. The lack of a drug interaction following single-dose administration does not predict the absence of an effect after chronic administration.
- **Cimetidine and ranitidine:** Concomitant use of zolpidem tartrate with cimetidine or ranitidine showed no significant pharmacokinetic interactions.
- **Digoxin:** Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

STATEMENT OF USAGE FOR HIGH-RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Zolpidem tartrate should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Studies in children to assess the effects of prenatal exposure to zolpidem tartrate have not been done; however, there have been case reports of severe neonatal respiratory depression when zolpidem tartrate was used at the end of pregnancy, particularly 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**.**

Labor and delivery/Lactation
There is no established use of zolpidem tartrate in labor and delivery**.**
Small quantities of zolpidem tartrate appear in breast milk. The use of zolpidem tartrate in breastfeeding mothers is therefore not recommended.

INFANTS AND CHILDREN
Safety and effectiveness of zolpidem tartrate in pediatric patients under 18 years old have not been established. Thus, zolpidem tartrate should not be prescribed in this population.

GERIATRIC
Adverse effects of zolpidem tartrate tend to be dose related, particularly in the elderly**.** The initial dose of zolpidem tartrate should be reduced to decrease the possibility of adverse effects. These patients also should be monitored closely**.**

PATIENTS WITH CONCOMITANT ILLNESS
Caution should be exercised in giving zolpidem tartrate in patients with diseases or conditions that could affect the metabolism or hemodynamic responses such as sleep apnea syndrome or myasthenia gravis.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS *(See Warnings and Precautions)*
Body as a Whole: Falls, allergy, allergic reaction, allergy aggravated, anaphylactic shock, edema, face edema, angioneurotic edema, back pain, influenza-like symptoms, pain, chest pain, pallor, asthenia, fatigue, fever, malaise, trauma, hot flashes, rigors, tolerance increased, infection, abscess herpes simplex herpes zoster
Cardiovascular: Palpitation, postural hypotension, hypotension, syncope, flushing, cerebrovascular disorder, hypertension, tachycardia, angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia
Endocrine metabolic: Impotence, decreased weight, increased appetite, decreased libido, hyperglycemia, thirst, gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema
Gastrointestinal: Diarrhea, dry mouth, abdominal pain, constipation, altered saliva, increased saliva, tenesmus, dyspepsia, hiccup, anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting, enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries
Hepatic: Abnormal hepatic function, increased serum concentrations of aspartate aminotransferase (AST) alanine aminotransferase (ALT), increased serum alkaline phosphatase, bilirubinemia
Hematologic: Increased erythrocyte sedimentation rate, anemia, hyperhemoglobinemia, leucopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis
Musculoskeletal: Arthralgia, myalgia, arthritis, arthrosis, muscle weakness, sciatica, tendinitis
Nervous System: Daytime drowsiness, drowsiness, dizziness, vertigo, amnesia, nausea, headache, drugged feelings, lethargy, lightheadedness, depression, irritability, restlessness, nightmare, sleep disorder, ataxia, confusion, euphoria, insomnia, agitation, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor, abnormal gait, abnormal thinking and behavior changes, aggressive reaction, apathy, anger, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, psychosis, suicide attempts, tetany, yawning
Reproductive/Urogenital: Menstrual disorder, vaginitis, breast fibroadenosis, breast neoplasm, breast pain, urinary tract infection, cystitis, urinary incontinence, acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention
Respiratory: Sinusitis, pharyngitis, upper respiratory infection, lower respiratory infection, bronchitis, coughing, dyspnea, rhinitis, bronchospasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia
Skin and appendages: Rash, increased sweating, flushing, pruritus, acne, bullous eruption, dermatitis, furunculosis, photosensitivity reaction, urticaria
Special senses: Abnormal accommodation, glaucoma, diplopia, vision abnormal, eye irritation, eye pain, scleritis, conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia, taste perversion, tinnitus, otitis externa, otitis media

OVERDOSAGE AND MANAGEMENT
Overdosage with zolpidem tartrate alone or in combination with CNS depressant agents resulted in impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes.
General symptomatic and supportive measures should be used along with immediate gastric lavage as necessary**.** Intravenous fluids should be given as needed. Flumazenil is shown to reduce zolpidem tartrate sedative hypnotic effect and therefore, may be useful; however, flumazenil's use may contribute to the appearance of neurological symptoms such as convulsions. Respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures should be employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Even if excitation occurs, sedating drugs should be withheld after zolpidem tartrate overdosage. The importance of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have shown zolpidem tartrate to be not dialyzable.
The possibility of multiple drug ingestion should be considered in the management of zolpidem tartrate overdosage.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Zolpidem Tartrate (Zoldem) 10 mg Film-coated tablet - Opaque white PVC/PVDC thermoforming film/aluminum foil blister strip x 10's (box of 30's)
DR-XY32230

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.
Dangerous Drug - to be prescribed in the personalized prescription form in triplicate copies by an S-2 licensed physician.

STORAGE
Store at temperatures not exceeding 30°C.

Trusted Quality Healthcare

Manufactured by
AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

P300000018663 Date of First Authorization: November 16, 2007 Date of Revision: August 2014 *Reg. IPOPHIL