PRODUCT MONOGRAPH

IVADAL™

(zolpidem tartrate)

10 mg Tablets

Hypnotic Agent

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NAME OF DRUG

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(zolpidem tartrate)
10 mg Tablets

THERAPEUTIC CLASS

Hypnotic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

IVADAL (zolpidem tartrate), an imidazopyridine derivative, is a short acting hypnotic agent. Zolpidem belongs to a novel chemical class, which is structurally unrelated to existing hypnotics. While zolpidem is a hypnotic agent with 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.

With hypnotic drugs, the duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) and beta (elimination) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairment of cognitive and motor performance during waking hours. If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated hypnotics: 1) increased wakefulness during the last third of the night and 2) the appearance of increased day-time anxiety (See WARNINGS).

Pharmacodynamics:
Subunit modulation of the $GABA_A$, receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxioytic, and myorelexant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.
While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines**,** barbiturates, or other drugs with known hypnotic properties, it interacts

with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which nonselectively bind to and activate all omega receptor subtypes, zolpidem, *in vitro* binds the (ω_1) receptor preferentially with a high affinity ratio of the $alpha_1$/$alpha_5$ subunits. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulate), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of the myrorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics:
The pharmacokinetic profile of IVADAL is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{½}$) in healthy subjects. In a single-dose crossover study in 45 healthy subjects administered 5- and 10-mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range: 29 to 113) and 121 (range: 58-272) ng/mL, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean IVADAL elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5-and 10-mg tablets, respectively. IVADAL is converted to inactive metabolites that are eliminated primarily by renal excretion. IVADAL demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20-mg zolpidem tartrate tablets for 2 weeks.

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

Elderly:
In the elderly, the dose for IVADAL should be 5 mg (See PRECAUTIONS and DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{½}$, and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (> 70 years), the means for C_{max}, $T_{½}$, and AUC significantly increased by 50% (255 vs 384 ng/mL), 32% (2.2 vs 2.9 hr) and 64% (955 vs 1,562 ng hr/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20-mg oral zolpidem dose. IVADAL did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Hepatic Insufficiency:
The pharmacokinetics of IVADAL in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem

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 normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with mild to moderate hepatic insufficiency. IVADAL has not been studied in patients with severe hepatic insufficiency (See CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency:
IVADAL pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl_{Cr}=6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max} half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{½}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{½}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng hr/mL after the first dose and 818 ± 170 ng hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 to 21 days.

Clinical Trials:

Transient Insomnia: Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n=35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5,10,15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakening, and sleep quality).

Chronic Insomnia: Adult outpatients with chronic insomnia (n=75) were evaluated in a double blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate (10

and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo of all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studies.

Adult outpatients (n=141) with chronic insomnia were evaluated in a double-blind parallel group, 4-week trial comparing two doses of zolpidem (10 and 15 mg) and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings and sleep quality for the first treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of sleep latency for the first 3 weeks, on a subjective measure of total sleep for the first week, and on the number of awakenings and sleep quality for the first two weeks.

Next day residual effects: There was no evidence of residual next-day effects seen with IVADAL (zolpidem tartrate) in several studies utilizing the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study. In another study involving elderly patients with chronic insomnia, there was no evidence of residual next-day effects utilizing DSST.

Rebound Effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of IVADAL. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory impairment: Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of IVADAL. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in-next-morning recall of information presented to subjects during peak drug effect 90 minutes post-dose, i.e., these subjects experienced anterograde amnesia. There was also subjective evidence form adverse event data for anterograde amnesia occurring in association with the administration of IVADAL, predominantly at doses above 10 mg.

Effects on Sleep Stages: In studies that measured the percentage of sleep time spent in each sleep stage, IVADAL has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found to be comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND CLINICAL USE

Since 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.

Adults:
IVADAL (zolpidem tartrate) is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

Treatment with IVADAL should usually not exceed 7 to 10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

Prescriptions for IVADAL should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

The use of hypnotics should be restricted for insomnia where disturbed sleep results impaired daytime functioning.

Geriatrics (≥ 65 years of age):
Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental events/falls. Therefore, the recommended IVADAL dosage is 5 mg in such patients (See PRECAUTIONS, Geriatrics; DOSAGE and ADMINISTRATION).

Pediatrics (< 18 years of age):
Safety and effectiveness of zolpidem in pediatric patients under the age of 18 years have not been established. Therefore, zolpidem should not be prescribed in this population (See PRECAUTIONS, Pediatrics; DOSAGE and ADMINISTRATION).

CONTRAINDICATIONS

IVADAL (zolpidem tartrate) is contraindicated in patients with a known hypersensitivity to the drug or any component of its formulation, severe hepatic insufficiency and in those with acute and/or severe impairment of respiratory function, e.g. significant sleep apnea syndrome.

IVADAL is contraindicated in patients with a personal or family history of sleepwalking.

WARNINGS

COMPLEX SLEEP-RELATED BEHAVIOURS:

Complex sleep-related behaviours 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 patients who have taken IVADAL. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with "sleep-driving", patients usually do not remember these events. Although complex sleep-related behaviours may occur with IVADAL alone at therapeutic doses, the use of alcohol and other CNS-depressants with IVADAL appears to increase the risk of such behaviours, as does the use of IVADAL at doses exceeding the maximum recommended dose.

- IVADAL is contraindicated in patients with a personal or family history of sleepwalking (see CONTRAINDICATIONS). Although complex-sleep behaviours have been reported in patients with or without history of sleepwalking, it is possible that some predisposed patients are at increased risk of experiencing these complex behaviours during treatment with IVADAL.
- IVADAL is not to be taken with alcohol.
- Caution is needed with concomitant use of other CNS depressants drugs (see DRUG INTERACTIONS).
- The use of IVADAL in patients with other disorders known to affect sleep and induce frequent awakenings (e.g. sleep apnea, Periodic Limb Movement Disorder, Restless Legs Syndrome) is discouraged, as they may be also at increased risk of complex sleep-related behaviours.
- Continuous use of IVADAL is limited to a short duration (see INDICATIONS, DOSAGE AND ADMINISTRATION).
- Patients should be instructed not to exceed the recommended dose.
- Caution should be exercised with concomitant use of potent CYP3A4 inhibitors (see DRUG INTERACTIONS).
- Due to the risk to the patient and the community, discontinuation of IVADAL should be strongly considered for patients who report any such complex sleep-related behaviours.

General:

Benzodiazepine and benzodiazepine-like compounds should be used with extreme caution in patients with a history of substance or alcohol abuse.

Because some of the important adverse effects of IVADAL (zolpidem tartrate) may be dose related, the smallest possible effective dose should be prescribed, especially for elderly patients.

Inappropriate heavy sedation in the elderly may result in accidental events/falls.

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness, which should be evaluated at regular intervals.

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 benzodiazepine and benzodiazepine-like drugs, including IVADAL.

IVADAL should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

Lactose is a non-medicinal ingredient in IVADAL. Patients with rare hereditary diseases of galactose intolerance (galactosemia or glucose-galactose malabsorption) should not take this medicine.

Severe Anaphylactic and Anaphylactoid Reactions:
Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including IVADAL. 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 IVADAL should not be rechallenged with the drug.

Use in Patients with Concomitant Illness:
Clinical experience with IVADAL in patients with concomitant systemic illness is limited.

Caution is advisable in using IVADAL in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of IVADAL in patients with normal respiratory function or in mild or moderate COPD (Chronic Obstructive Pulmonary Disease), precautions should be observed if IVADAL is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post -marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. IVADAL should be used with caution in patients with sleep apnea syndrome. IVADAL is contraindicated in patients with acute and/or severe respiratory impairment, e.g. significant apnea syndrome (See CONTRAINDICATIONS).

Data in end-stage renal failure patients repeatedly treated with IVADAL did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (See ACTIONS AND CLINICAL PHARMACOLOGY).

A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored. IVADAL is contraindicated in patients with severe hepatic insufficiency (See ACTIONS AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

IVADAL should be used with caution in patients who have myasthenia gravis.

Pregnancy:
Benzodiazepines may cause fetal damage when administered during pregnancy. During the first trimester of pregnancy, several studies have suggested an increased risk of congenital malformations associated with the use of benzodiazepines.

There are no adequate and well-controlled studies in pregnant women. IVADAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. As a precautionary measure, it is preferable to avoid the use of IVADAL during pregnancy.

If IVADAL is prescribed to a woman of child-bearing potential, the patient should be warned of the potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become pregnant or suspects that she is pregnant.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs during the late phase of pregnancy or during labor may be at some risk for physical dependence and withdrawal symptoms from the drug during the postnatal period. Effects on the neonate such as hypothermia and moderate respiratory depression can be expected due to the pharmacological action of the product. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

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.

Amnesia:
Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepine and benzodiazepine-like hypnotics. The event is rare with IVADAL. Anterograde amnesia is a dose related phenomenon and elderly subjects may be at particular risk. Cases of transient global amnesia and "traveller's amnesia" have also been reported in association with benzodiazepines, the latter in individuals who have taken the drug often in the middle of the night, to induce sleep while traveling. Transient global amnesia and traveler's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take IVADAL under circumstances in which a full night's sleep (7-8 hours) and clearance of the drug from the body are not possible before they need to resume full activity.

Abnormal Thinking and other Psychiatric Behavioral Changes:
A variety of abnormal thinking and other behavior changes have been reported to occur in association with the use of compounds that interact with the benzodiazepine receptors, including IVADAL, although rarely. Some of these changes may be characterized by decreased inhibition (eg. aggression and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Psychotic behavioral changes have included abnormal behavior, irritability, hallucination, anger, nightmare and depersonalization. Other neuropsychiatric symptoms may occur unpredictably. Abnormal behaviors associated with the use of benzodiazepines or benzodiazepine-like agents have been reported more with chronic use and/or high doses but they may occur during the acute, maintenance or withdrawal phases of treatment.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are 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. Should these occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations.

Cognitive Function:
Benzodiazepines and benzodiazepine-like compounds may affect concentration, attention and vigilance. This risk is greater in the elderly and in patients with cerebral impairment.

Complex sleep-related behaviours:
See boxed WARNINGS: COMPLEX SLEEP-RELATED BEHAVIOURS.

Depression:
Although no clinically significant pharmacokinetic and pharmacodynamic interactions with Selective Serotonin Reuptake Inhibitors (SSRIs) have been demonstrated (See DRUG INTERACTIONS section), as with other sedative/hypnotic drugs, caution should be exercised if IVADAL is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g. intentional overdose) is high in patients with depression and thus the least amount of IVADAL that is feasible should be available to them at any one time. Pre-existing depression may be unmasked during use of IVADAL. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

Psychomotor Effects:
IVADAL, like other hypnotic/sedative drugs, has CNS-depressant effects. Due to the rapid onset of action, IVADAL should only be ingested **immediately prior to going to bed**.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of IVADAL. In order to minimize this risk a full night sleep (7-8h) is recommended.

IVADAL showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when IVADAL is administered with such agents because of the potentially additive effects.

Anxiety/Restlessness:
Although not seen with IVADAL to date, an increase in daytime anxiety and/or restlessness has been observed during treatment with other hypnotics with a short elimination half-life. This is believed to be due to interdose withdrawal.

PRECAUTIONS

Abuse:
Studies of abuse potential in former drug abusers found that the effects of single doses of IVADAL 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

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

Dependence:
Use of sedative/hypnotic agents like IVADAL may lead to the development of physical and psychological dependence. When IVADAL is used in accordance with the recommendations for dosage, duration of treatment and warnings, the risk of withdrawal symptoms or rebound phenomena occurring is minimal. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or history of addiction to, or abuse of, drugs or alcohol. Tolerance, withdrawal or rebound phenomena have been observed when using IVADAL outside recommendations for use in these patients. As with any other hypnotic, these patients should be under careful surveillance when receiving IVADAL.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. Benzodiazepine and benzodiazepine-like agents 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.

Other symptoms include headache, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures.

The following possible withdrawal symptoms were reported during 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. Consequently, abrupt discontinuation should be avoided and a gradual dosage-tapering schedule is recommended for patients taking the drug for more than a few weeks.

Rebound Insomnia:
A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur when the medicinal product is discontinued.

In the case of benzodiazepine and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval.

As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

Psychotic Illness:
Hypnotics such as IVADAL are not recommended for the primary treatment of psychotic illness.

Labor and Delivery:
IVADAL has no established use in labor and delivery.

Nursing Mothers:
Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6 ± 0.3 hr). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown. The use of IVADAL in nursing mothers is not recommended.

Pediatrics (< 18 years of age):
Safety and effectiveness of zolpidem have not been established in patients below the age of 18 years. Therefore, zolpidem should not be prescribed in this population. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) (see DOSAGE AND ADMINISTRATION, Pediatrics).

Geriatrics (≥ 65 years of age):
Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental events/falls. Therefore, the recommended IVADAL dosage is 5 mg in such patients (See DOSAGE and ADMINISTRATION section).

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 mg or placebo, there were three adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses > 10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were ≥ 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

DRUG INTERACTIONS

Alcohol:
Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol (see WARNINGS, Complex-sleep related behaviours). This affects the ability to drive or use machines.

CNS-Active Drugs:
Since systemic evaluations of zolpidem tartrate in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with IVADAL.

IVADAL may produce additive CNS depressant effects when co-administered with sedative antihistamines, anticonvulsants, narcotic analgesics, anesthetics or psychotropic medications (as antipsychotics (neuroleptics), hypnotics, anxiolytics, sedatives and antidepressant agents) which themselves produce CNS depression. However, In the case of SSRI antidepressant agents (fluoxetine and sertraline), no clinical significant pharmacokinetic or pharmacodynamic interactions have been observed. In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

Drugs Affecting Cytochrome P450 Enzymes:
Compounds which inhibit cytochrome P450 may enhance the activity of some hypnotics like IVADAL. Zolpidem is metabolized via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2.

CYP 3A4 Inducer: The pharmacodynamic effect of zolpidem is decreased when it is administered with rifampicin (a CYP3A4 inducer).

CYP 3A4 Inhibitor:
A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem.

Co-administration of a single 5 mg dose of zolpidem and ketoconazole (200 mg twice daily for 2 days), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to IVADAL plus placebo. Co-administration with ketoconazole caused an increase in the AUC (67%) and C_{max} (35%) of zolpidem and enhanced the pharmacodynamic effects of zolpidem.

The use of IVADAL with ketoconazole or other potent CYP3A4 inhibitors may enhance sedation and other effects of the drug (see WARNINGS, COMPLEX SLEEP-RELATED BEHAVIOURS). If used concomitantly with potent CYP3A4 inhibitors, caution should be exercised. Consideration should be given to using a lower dose of IVADAL.

Other drugs:
Co-administration of cimetidine / zolpidem and ranitidine / zolpidem had no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however no significant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory Test Interactions:
Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids or amphetamines in two standard urine drug screens.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment: Approximately 4%, of 1,701 patients who received zolpidem at all doses in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses in similar non-U.S. trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1,1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Most Commonly Observed Adverse Events in Controlled Trials:
During short-term treatment (up to 10 nights) with IVADAL (zolpidem tartrate) at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%)
and drugged feelings (3%).

Adverse Events Observed at an Incidence of ≥ 1% in Controlled Trials:

Adults
The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence of at least 1% and at greater frequency than in the placebo group among patients with insomnia who received IVADAL in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studies.

The following table was derived from a pool of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

Incidence of Treatment-Emergent Adverse Experiences (1% and higher than placebo) in
Short-term Placebo-Controlled Clinical Trials in Adults
(Percentage of patients reporting)

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

Diarrhea	1	–

The following table was derived from a pool of three placebo-controlled long-term efficacy trials involving IVADAL. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients and at greater frequency than in the placebo group.

Incidence of Treatment-Emergent Adverse Experiences (1% and higher than placebo) in Long-term Placebo-Controlled Clinical Trials in Adults (Percentage of patients reporting)

Body System/ Adverse Event	**Zolpidem (≤ 10 mg) (N=152)**	**Placebo (N=161)**
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	--
Chest pain	1	--
Cardiovascular System		
Palpitation	2	--
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	--
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	--
Amnesia	1	--
Sleep disorder	1	--
Gastrointestinal System		
Diarrhea	3	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

Pediatrics

Adverse Events Observed in Children with Insomnia associated with ADHD:
The following table was derived from an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD). In this study, psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) (see PRECAUTIONS, Pediatrics and DOSAGE AND ADMINISTRATION, Pediatrics).

Incidence (%) of Treatment-Emergent Adverse Experiences (1% and higher than placebo) in a Placebo-Controlled Clinical Trials in children with insomnia associated with ADHD

Body System/ Adverse Event	**Zolpidem (N=136)**	**Placebo (N=65)**
Eye Disorders		
Diplopia	2.2	0
Gastrointestinal Disorders		
Diarrhea	2.9	1.5
Infections and infestations		
Nasopharyngitis	2.9	1.5
Gastroenteritis	2.9	0
Ear infection	1.5	0
Gastroenteritis viral	1.5	0
Meningitis viral	1.5	0
Pharyngitis streptococcal	1.5	0
Injury, Poisoning and Procedural Complications		
Fall	2.9	1.5
Excoriation	2.2	1.5
Injury	2.2	1.5
Joint sprain	1.5	0
Nervous System Disorders		
Dizziness	23.5	1.5
Headache	12.5	9.2
Drooling	1.5	0
Dysgeusia	1.5	0
Memory impairment	1.5	0
Tremor	1.5	0
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	1.5	0
Psychiatric Disorders		
Affect lability	2.9	0
Hallucination, visual	2.9	0
Anxiety	2.2	0

Body System/ Adverse Event	Zolpidem (N=136)	Placebo (N=65)
Hallucination	2.2	0
Hypnagogic hallucination	2.2	0
Sleep walking	2.2	0
Abnormal dreams	1.5	0
Disorientation	1.5	0
Renal and Urinary Disorders		
Enuresis	2.9	0

Dose Relationship for Adverse Events:
There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events. Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination.

Adverse Event Incidence Across the Entire Preapproval Database:
IVADAL 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 IVADAL, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic nervous system:
Infrequent: increased sweating, pallor, postural hypotension, syncope.
Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole:

Frequent: asthenia, fatigue
Infrequent: edema, falling, fever, malaise, and trauma.
Rare: allergic reaction, allergy aggravated, abdominal body sensation, 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: anxiety, ataxia, confusion, euphoria, headache, insomnia, nervousness vertigo.
Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional Iability, hallucination, hypoesthesia, illusion, leg cramps, migraine, 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 (See WARNINGS, Complex sleep-related behaviours), suicide attempts, tetany, yawning.

Gastrointestinal system:
Frequent: abdominal pain, anorexia, dyspepsia, hiccup, nausea, vomiting.
Infrequent: constipation, dysphagia, flatulence, gastroenteritis.
Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system:
Rare: anemia, hyperhemoglobulinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system:
Frequent: Infection.
Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and biliary system:
Infrequent: abnormal hepatic function, increased SGPT.
Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional:
Infrequent: hyperglycemia, thirst.
Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal system:
Frequent: arthralgia, myalgia.
Infrequent: arthritis.
Rare: arthrosis, muscle weakness, sciatica, tendinitis.

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

Respiratory system:
Frequent: rhinitis, upper respiratory infection.
Infrequent: bronchitis, coughing, dyspnea.
Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

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

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

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

Postmarket Experience:
Postmarket reports of skin reactions have been reported, such as angioneurotic oedema, rash, urticaria, pruritus, and hyperhidrosis.

Cases of depressed level of consciousness have been reported, mainly in the context of a drug overdose or misuse, including high doses in elderly patients (10 mg), and also with zolpidem taken at recommended doses, mostly with concomitant CNS-depressants or CYP3A4 inhibitors or substrates. A few cases of depressed level of consciousness were reported in patients taking zolpidem alone at recommended doses.

SYMPTOMS AND TREATMENT OF OVERDOSE

Signs and Symptoms:
In cases of overdose involving zolpidem alone or with other CNS-depressant agents (including alcohol), impairment of consciousness up to coma, and more severe symptomatology, including fatal outcomes have been reported.

Recommended Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Intravenous fluids should be administered as needed.

Flumazenil (Anexate®) is a benzodiazepine antagonist that is used as a specific antidote in known or suspected overdose with benzodiazepines or benzodiazepine-like agents. (For conditions of use see Anexate Product Monograph). Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (agitation, anxiety, and 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 IVADAL is not dialyzable.

Poison Control Center:
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.

DOSAGE AND ADMINISTRATION

As with all hypnotics, long-term use of IVADAL is not recommended. Treatment with IVADAL (zolpidem tartrate) should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

IVADAL is for oral use only. If a 5 mg dose is prescribed, patients should be instructed to split the 10 mg tablet in the score line.

Adult Dose:
The recommended daily dose for adults is 10 mg.
IVADAL acts rapidly and therefore should be taken immediately before retiring, or in bed.

Downward dosage adjustments may be necessary when IVADAL is administered with agents having known CNS-depressant effects because of the potentially additive effects (See DRUG INTERACTIONS section).

Pediatrics (< 18 years of age):
Safety and effectiveness of IVADAL in pediatric patients under the age of 18 years have not been established. Therefore, IVADAL should not be prescribed in this population (see PRECAUTIONS: Pediatric Patients).

Geriatric (≥ 65 years of age):
Since elderly or debilitated patients may be especially sensitive to the effects of IVADAL, a 5 mg dose (one-half of a 10 mg tablet) is recommended in these subjects. The total IVADAL dose should not exceed 10 mg in this population.

Hepatic impairment:
As clearance and metabolism of IVADAL is reduced in hepatic impairment, dosage should begin at 5 mg (one-half of a 10 mg tablet) in patients with mild to moderate hepatic impairment, with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated. IVADAL is contraindicated in severe hepatic impairment (See CONTRAINDICATIONS).

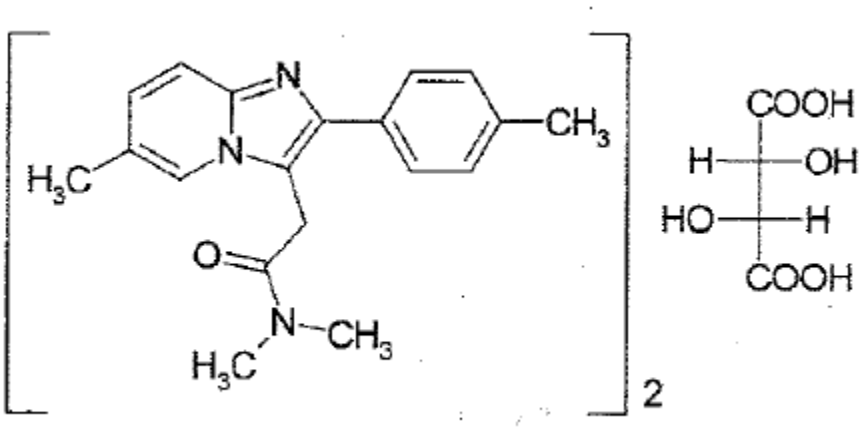
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Zolpidem tartrate (U.S.A.N.)

Chemical Name: 2-(4-Methylphenyl)-N,N,6-trimethylimidazo [1,2-a]pyridine-3-acetamide tartrate (2:1)

Structural Formula:



Molecular Weight: 764.88

Molecular Formula: $(C_{19}H_{21}N_30)_2$-$C_4H_6O_6$ OR $C_{42}H_{48}N_6O_8$

Description:

Appearance: White to off-white, odorless, microcrystalline powder

Melting point: 193-197º C

Solubility: Sparingly soluble in water (23 mg/ml at 20ºC)
(Solubility has been determined over the pH range 1-10 at 37ºC)

pKa: 6.2

pH: 4.0-5.5 (1% aqueous suspension)

Partition Coefficient: 2.42 (octano/water at pH 7.4)

Composition:
Each 10 mg tablet contains 10 mg zolpidem tartrate. Non-medicinal ingredients: cellulose, hypromellose, lactose, magnesium stearate, sodium starch glycolate. Film coating contains hypromellose, macrogol 400 and titanium dioxide. The 10 mg tablet can be split into two equal parts of 5 mg.

Storage:
Store at 15 – 30ºC.

AVAILABILITY

IVADAL 10 mg is available as while to off-white, film coated oblong tablets, scored and engraved with SN10 on one side and the supplied in blister strips of 10 tablets to yield 30, 100 or 150 tablets per carton.

IVADAL™
(zolpidem tartrate)

INFORMATION FOR THE PATIENT

What is the most important information I should know about IVADAL?
There have been reports of people getting out of bed while not fully awake after taking IVADAL and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behavior is more likely to occur when IVADAL is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

IMPORTANT:

1. Do not take more IVADAL than prescribed.
2. Do not take IVADAL if you drink alcohol.
3. Do not take IVADAL if you have had episodes of sleepwalking in the past, or if there is a history of sleepwalking in your family.
4. Talk to your doctor if you have a condition that affects your sleep, such as Periodic Limb Movement in Sleep (involuntary movement of limbs during sleep) or Restless Legs Syndrome (urge to move legs, usually accompanied by uncomfortable and unpleasant sensations, that begins or worsens during periods of inactivity, typically in the evening and night)
5. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take IVADAL with your other medicines.
6. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done *any* such activities for which you have no memory you should call your doctor immediately.

INTRODUCTION

IVADAL is intended to help you sleep. It is one of several prescription sleeping pills that have generally similar properties.

If you are prescribed one of these medications, you should consider both their benefits and risks. Important risks and limitations include the following:

- the medication may cause dependence;
- the medication may affect your mental alertness or memory, particularly when not taken as prescribed

In order to guide you in the safe use of the product, this leaflet will inform you about this class of medication in general and about IVADAL in particular.

BUT THIS LEAFLET SHOULD NOT REPLACE A DISCUSSION BETWEEN YOU AND YOUR DOCTOR ABOUT THE RISK AND BENEFITS OF IVADAL.

INFORMATION FOR PATIENTS TAKING IVADAL

Your doctor has prescribed IVADAL to help you sleep. The following information is intended to guide you in the safe use of this medicine. It is not meant to take the place of your doctor's instructions. If you have any questions about IVADAL tablets be sure to ask your doctor or pharmacist.

What you should know about IVADAL:
IVADAL is used to treat different types of sleep problems, such as:
- Trouble in falling asleep
- waking up too early in the morning
- waking up often during the night

IVADAL belongs to a group of medicines known as the sedatives or simply, sleep medicines. There are many different sleep medicines available to help people sleep better. IV ADAL is used to treat difficulty in falling asleep. IVADAL works very quickly and has its effect during the first part of the night, since it is rapidly eliminated by the body.

How can IVADAL help?
Your doctor has prescribed IVADAL to help you sleep. Sleep problems are usually temporary, requiring treatment for only a short time, usually from a few days up to a few weeks. Some people have chronic sleep problems that may require more prolonged use of sleep medicine. However, you should not use these medicines for long periods without talking with your doctor about the risks and benefits of prolonged use. If you still have problems sleeping after you have finished your tablets, contact your doctor again.

Before taking IVADAL:
Tell your doctor if you are or intend to become pregnant, or if you are breast-feeding.
Discuss with your doctor if you have:
- had a bad reaction to zolpidem in the past
- breathing difficulties
- sleep apnea (stopping breathing for short periods while asleep)
- liver disease
- had problems with drug addiction
- had problems with alcohol abuse
- myasthenia gravis
- conditions that affect your sleep such as Periodic Limb Movement in Sleep (involuntary movement of limbs during sleep) or Restless Legs Syndrome (urge to move legs, usually accompanied by uncomfortable and unpleasant sensations, that begins or worsens during periods of inactivity, typically in the evening and night)

If you are in doubt about whether you have any of these conditions, do ask your doctor.

Inform your doctor or pharmacist about all of your medicines, including over-the-counter medicines and herbal products. Some of the drugs that may interact with IVADAL are: Nizoral® (ketoconazole) and Sporanox® (itraconazole) for fungal infections, antivirals such as ritonavir, and antibiotic such as clarithromycin.

How to take IVADAL:

- Take the exact dose that the doctor has prescribed. Do not change it without talking to your doctor first.
- If you are prescribed a 5 mg dose, you must take one-half of a 10 mg tablet divided in two equal parts at the score line.
- Swallow the tablet (or half-tablet) with a glass of water.
- You should only take zolpidem when you are ready to get into bed and go to sleep, or once in bed and have not been able to fall asleep.
- If you forget to take your tablet at bedtime, do not take it at any other time, otherwise you may feel drowsy, dizzy and confused during the day; do not take a double dose to make up for the missed dose.

For IVADAL to help you fall asleep you should not take it with or immediately after a meal.

When not to take IVADAL:

- Do not take IVADAL if you are allergic to it or any of the components of its formulation (see What does IVADAL contain?). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.
- Do not take IVADAL if you have a muscular disease that causes muscle weakness known as myasthenia gravis
- Do not take IVADAL if you have severe liver problems.
- Do not take IVADAL if you have severe lung or respiratory disease, including sleep apnea (you stop breathing for short periods during sleep).
- Do not take IVADAL if you have had episodes of sleepwalking in the past, or if there is a history of sleepwalking in your family
- Avoid alcohol while using IVADAL or any other sleep medicine.
- Do not use IVADAL along with other medications without talking to your doctor first. This includes medicines that you can buy without a prescription.
- Children under 18 years of age should not take IVADAL.

SIDE EFFECTS

Most common side effects:
All medicines have side effects. Most common side effects of sleep medicines include: drowsiness, dizziness, lightheadedness and difficulty with coordination.

Consult your doctor if you experience these or other side effects, as dose may have to be adjusted.

Allergic reactions:
Rare cases of severe allergic reactions have been reported. Symptoms may include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking IVADAL.

You may find that these medicines make you sleepy during the day. How drowsy you feel depends upon how your body reacts to the medicine, which sleep medicine you are taking, and how large a dose your doctor has prescribed. Daytime drowsiness is best avoided by taking the lowest dose possible that will still help you sleep at night. Your doctor will work with you to find the dose of IVADAL that is best for you.

SPECIAL CONCERNS

There are some special problems that may occur while taking sleep medicines.

Memory problems:
Sleep medicines may cause a special type of memory loss or "amnesia." When this occurs, a person may not remember what has happened for several hours after taking the medicine. This is usually not a problem since most people fall asleep after taking the medicine.

But it can be a problem when sleep medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia."

Memory problems are not common while taking IVADAL. In most instances memory problems can be avoided if you take IVADAL only when you are able to get a full night's sleep (7 to 8 hours) before you need to be active again. Be sure to talk to your doctor if you think you are having memory problems.

Tolerance:
When sleep medicines are used every night for more than a few weeks, they may lose their effectiveness to help you sleep. This is known as "tolerance." If your sleep problems continue, consult your doctor, who will determine whether other measures are needed to overcome your sleep problems.

Withdrawal:
Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used daily for a long time. Usually these withdrawal effects are more common and severe after long periods of continued use.

Another problem that may occur when sleep medicines are stopped is known as "rebound insomnia." This means that a person may have more trouble sleeping the first few nights after the medicine is stopped than before starting the medicine. If you should experience rebound insomnia, do not get discouraged. This problem usually goes away on its own after 1 or 2 nights.

In mild cases, withdrawal symptoms may include unpleasant feelings. In more severe cases, abdominal and muscle cramps, vomiting, sweating, shakiness, and rarely, seizures may occur. These more severe withdrawal symptoms are very uncommon.
If you have been taking IVADAL or any other sleep medicine for more than 1 or 2 weeks, do not stop taking it on your own. Always follow your doctor's directions.

Dependence:
All sleep medicines can cause dependence, especially when these medicines are used regularly for longer than a few weeks or at high doses. Some people develop a need to continue taking their medicines. This is known as dependence or "addiction".

When people develop dependence, they may have difficulty stopping the sleep medicine. If the medicine is suddenly stopped, the body is not able to function normally and unpleasant symptoms (see *Withdrawal)* may occur. They may find they have to keep taking the medicine either at the prescribed dose or at increasing doses just to avoid withdrawal symptoms.

All people taking sleep medicines have some risk of becoming dependent on the medicine. However, people who have been dependent on alcohol or other drugs in the past may have a higher chance of becoming addicted to sleep medicines. This possibility must be considered before using these medicines for more than a few weeks.

If you have been addicted to alcohol or drugs in the past, it is important to tell your doctor before starting IVADAL or any sleep medicine.

Changes in behavior and thinking:
Some people using sleep medicines have experienced unusual changes in their thinking and/or behavior. These effects are not common. However, they have included:
- more outgoing or aggressive behavior than normal
- loss of personal identity, feeling like you are not yourself
- confusion
- strange behavior
- sleep walking and other associated behaviours such as sleep driving and eating food
- agitation or restlessness
- hallucinations

- worsening of depression
- suicidal thoughts

How often these effects occur depends on several factors, such as a person's general health, the use of other medicines, and which sleep medicine is being used. Clinical experience with IVADAL suggests that it is uncommonly associated with these behavior changes.

It is also important to realize that it is rarely clear whether these behavior changes are caused by the medicine, an illness, or occurs on their own. In fact, sleep problems that do not improve may be due to illnesses that were present before the medicine was used. If you or your family notice any changes in your behavior, or if you have any unusual or disturbing thoughts, call your doctor immediately.

Pregnancy and Breast-feeding:
Sleep medicines may cause sedation of the unborn baby when used during the last weeks of pregnancy. *Therefore, IVADAL is not recommended for use during pregnancy.*

Certain benzodiazepine sleep medicines have been linked to birth defects when taken during the early months of pregnancy. It is not yet known if zolpidem could cause similar effects.

Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking IVADAL.

After use of the medicine, a very small amount of zolpidem may be present in breast milk. Its effects on an infant are unknown, therefore the use of IVADAL in nursing mothers is not recommended.

IVADAL is Not Recommended for Use During Pregnancy

SAFE USE OF SLEEPING MEDICINES

To ensure the safe and effective use of IVADAL or any other sleep medicine, you should observe the following cautions:

1. IVADAL is a prescription medicine and should be used ONLY as directed by your doctor. Follow your doctor's instructions about how to take, when to take, and how long to take IVADAL.

2. Never use IVADAL or any other sleep medicine for longer than directed by your doctor.

3. If you notice any unusual and/or disturbing thoughts or behavior during treatment with IVADAL or any other sleep medicine, contact your doctor.

4. Tell your doctor about any medicines you may be taking, including medicines you

may buy without a prescription. You should also tell your doctor if you drink alcohol. DO NOT use alcohol while taking IVADAL or any other sleep medicine.

5. Do not take IVADAL unless you are able to get a full night's sleep before you must be active again. For example, IVADAL should not be taken on an overnight airplane flight of less than 7 to 8 hours since "traveler's amnesia" may occur.

6. Do not increase the prescribed dose of IVADAL or any other sleep medicine unless instructed by your doctor. Do not take a second dose within a single night.

7. When you first start taking IVADAL or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft.

8. Be aware that you may have more sleeping problems the first night or two after stopping any sleep medicine.

9. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking IVADAL. Taking IVADAL at any time during pregnancy is not recommended.

10. As with all prescription medicines, never share IVADAL or any other sleep medicine with anyone else. Always store IVADAL or any other sleep medicine in the original container out of reach of children.

11. IVADAL works very quickly. You should only take IVADAL right before going to bed and are ready to go to sleep.

What does IVADAL contain?
IVADAL is available in tablets containing 10 mg zolpidem tartrate as active ingredient. Non-medicinal ingredients include: cellulose, hypromellose, lactose, macrogol 400, magnesium stearate, sodium starch glycolate and titanium dioxide.

What to do if you take too many tablets?
Contact your doctor, a Poison information centre or the nearest hospital emergency department, even though you do not feel sick.

Reminder
This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions about its use, ask your doctor or pharmacist.

Storage Instructions: Store at room temperature 15 to 30° C.

PHARMACOLOGY

In vitro: Zolpidem is an imidazopyridine whose mechanism and site of action have been established in rodent studies. Zolpidem differs from benzodiazepine hypnotics in that it shows a high affinity for the central BZD_1 ($omega_1$) receptor subtype with no affinity for central BZD_2 ($omega_2$) receptor subtype.

It is four times more potent in inhibiting the binding of labeled diazepam at cerebellar sites than at hippocampal sites. Labeled zolpidem shows preferential binding for BZD_1, receptors in the substania nigra, the ventral pallidum, the cerebral cortex and the cerebellum.

Concentrations are negligible in areas rich in BZD_2 receptors, such as the striatum, nucleus accubens and dentate gyrus, and no binding is seen in the spinal cord. Like diazepam, zolpidem binding is increased by GABA and by the presence of chloride ions. At hypnotic doses, zolpidem does not significantly alter cerebral noradrenaline metabolism in the rat; it decreases cerebellar cGMP levels, but this effect is of short duration.

In vivo: Zolpidem also shows anticonvulsant, anxiolytic and muscle relaxant activity in several models, but only at doses above those that are hypnotic.

Zolpidem induces slow wave sleep in the immobilized rat at doses of 0.1-1.0 mg/kg i.p. or p.o. This activity appears rapidly and disappears after a brief period. There is no evidence of the development of tolerance during administration for up to eight days.

Administration of benzodiazepine hypnotics in the immobilized cat ordinarily will induce a predominantly rapid EEG rhythm. Zolpidem caused less disruption of the normal pattern and produced deep sleep at doses of 0.1 - 10 mg/kg i.v. in relation to five such drugs to which it was compared. In the anesthetized monkey, doses of 0.3 - 3 mg/kg i.v. accentuate the presence of slow waves in cortical recordings.

In the freely moving implanted rat, zolpidem exhibits the effects of a rapidly acting hypnotic in recordings made during the period of light and during the period of darkness or following pCPA pre-treatment. Doses of 0.3 - 3 mg/kg p.o. increased both classical sleep and paradoxical sleep. The duration of action ranged between one and three hours; in this model midazolam's effect lasts four hours. Neither drug showed a sedative effect 24 hours after administration, and an increase in arousal was noted in the animals treated with zolpidem at this point.

In the freely moving implanted cat, zolpidem induces a short period of agitation following a dose of 1 mg/kg p.o. similar to that seen following benzodiazepine administration, but the total duration of the sleep phases and the duration of paradoxical sleep are not changed. Doses of 3 and 10 mg/kg p.o. (15-50 X HTD) increase the total time of wakefulness in the cat. Rebound insomnia was seen following triazolam after 24 hours, but not with zolpidem, which appears to cause less agitation than the

benzodiazepines and does not induce rapid cortical rhythms.

In effects on motor activity, zolpidem is equal in potency to midazolam. Zolpidem is less active in decreasing muscle strength than triazolam or midazolam. Midazolam is six times more potent than zolpidem in causing motor incoordination. In effects on spinal reflexes, triazolam is eighty times (and diazepam four or five times) more potent than zolpidem. Zolpidem i.p. decreases the acquisition of conditioned fear in the mouse, but oral dosing produces no effect.

In rats trained to discriminate between chlordiazepoxide and saline (i.p.), zolpidem generally triggered the same response as saline. In discriminant tests in monkeys. zolpidem ranks below chlordiazepoxide and equal to saline. Zolpidem discrimination appears to be correlated with sedation.

Dependence potential has been studied in two models in the cynomolgus monkey. Monkeys were examined for signs of the abstinence syndrome after two weeks at 10 and two weeks at 20 mg/kg p.o. twice daily. After a week off the drug (week 5), zolpidem was reintroduced at 20 mg/kg twice daily during the sixth to ninth weeks, and evidence of an abstinence syndrome was sought during the tenth week off drug. These doses induced mild behavioral depressant effects. To obtain an equivalent effect at the beginning and end of the experiment, the zolpidem dose had to be doubled whereas that of triazolam had to be increased twenty-fold. In the second model, monkeys could self-administer intragastric doses of zolpidem by pressing a lever. It was concluded that zolpidem causes a slight abstinence syndrome and induces slight self-administration behavior with a high degree of variability between animals tested.

Zolpidem 50 mg/kg p.o. does not alter blood pressure or baseline heart rate in the anesthetized normotensive rat. In the pithed normotensive rat, zolpidem does not interact with the alpha- or beta-adrenoceptors, or with serotonergic or muscarinic receptors. Zolpidem i.v. produced bradycardia and severe sedation in the conscious rabbit. In the anesthetized dog with a denervated heart, doses up to 0.3 mg/kg i.v. do not cause any significant change in various hemodynamic measures. At 3 mg/kg i.v., zolpidem reduces aortic pressure in dogs with neurologically normal hearts, and the bradycardia observed at lower doses is replaced by reflex tachycardia. Coronary output decreased in three of five dogs after these doses.

Zolpidem shows major peripheral analgesic activity in the acetic acid test in the mouse, but its activity in the hotplate test is very slight. Its anti-inflammatory activity is equal to that of ibuprofen. In the rat, zolpidem exhibits no platelet antiaggregant activity. In an *in vitro* test on rabbit platelets versus collagen, the activity of zolpidem is one-half that of aspirin and equals that of dipyridamole.

In the urethane-anesthetized rat, zolpidem 10 mg/kg i.v. does not cause any significant change in respiratory rate, respiratory minute flow volume or pulmonary resistance.

TOXICOLOGY

Acute Toxicity:

Species/ Route	LD_{60} mg/kg	Signs of Toxicity
Mouse p.o.	2160 (1614 - 2786) m 2320 (1622-3318) f	Deaths 3-24 hr., hypomotility, ataxia, ptosis, dyspnea, bradypnea, apnea, cyanosis clonic convulsion.
Mouse i.p.	472 (403-552) m 444 (386-510) f	Hypomotility, prostration, tremors, startle reactions, polypnea, apnea, dyspnea, cyanosis.
Mouse i.v.	100 (83-115) m 128 (114-145) f	Sleep lethargy, piloerection, tremors, slight sporadic clonic convulsions.
Rat p.o.	556 (456 - 678) m 824 (710-956) f	Ataxia, ptosis, prostration, sleep, lacrymation, polypnea, dyspnea, startle reactions, chewing
Rat i.p.	488 (428-556) m 464 (422-510) f	Ataxia, lacrymation, polypnea, dyspnea, apnea, lethargy.
Rat i.v.	70 (66-75) m 96 (72-129) f	Sleep, prostration. jerks, piloerection chewing in females.

Long-term Toxicity:

Species/Route		Dosage mg/kg/day	Signs of Toxicity
Rat p.o. 1 week	(m,f)	500, 1000	Narcosis, sedation, chewing, ptosis, sialorrhea, piloerection
Rat p.o. 4 weeks	(m,f)	10, 50, 200	Sedation and hypotonia preceded by hyperactivity. At 50 and 200 mg also respiratory difficulties, chewing movement, increased thyroid, liver, kidney, ovary and adrenal weights. Decreased weight gain and food consumption. Increased urine and reticulocytes in high-dose females.
Rat p.o. 13 weeks and 4 week reversibilty	(m,f)	5, 25, 125	5 mortalities at 125 mg, 1 mortality at 25 mg. Hypomotility, prostration, drowsiness, hypersalivation, stereotyped movements, somnolence. Decreased weight gain and food consumption. Reversible increased liver weights in high-dose males and females.
Rat p.o. 52 weeks	(m,f)	5, 25, 125	Mortalities: 3 at 5 mg, 5 at 25 mg and 12 at 125 mg. Transient collapsed posture, unsteady gait. Weight gain decreased in males at 25 and 125 mg, and in females at 25 mg increased in females at 125 mg. Food intake increased. At 125 mg: lower RBC counts for males, decreased Hb for females, increased cholesterol and urine voided in females, increased adrenal and liver weights: enlarged adrenals in 6 females; increased incidences of basophilic hepatocytes in females.
Monkey p.o. 9 days	(m,f)	50, 75,100,150 200	Signs reflective of pharmacologic action of drug, motor in coordination, sleep-like state, awareness retained but cutaneous sensitivity lost.
Monkey p.o. 4 weeks	(m,f)	5, 30, 180	Dose dependent sedation leading to narcosis in the high dose
Monkey p.o. 13 weeks	(m,f)	5, 25,125	Dose dependent ptosis of upper eyelid, somnolence, incoordination, body tremor, jerky body movements. Transient reduced RBC values at highest dose weeks 6 and 12.
Monkey 52 weeks	(m.f)	5, 25,125	Dose dependent subdued behaviour, ptosis, limb tremors, prostration. Increased mean body weights for males

			at 25 and 125 mg. Increased pituitary weights at interim sacrifice only at high dose; changes no longer apparent at termination.

Carcinogenicity:

Species/Route	Dosage mg/kg/day	Signs of Toxicity
Mouse, diet 104 weeks	4, 18, 80	Percent Survival Rates: 4 mg: Males 38. Females 48 18 mg: Males 23. Females 50 80 mg: Males 29, Females 65 Increased mean WBC count in high dose males due to one mouse with high lymphocyte and neutrophil counts. Age related increases in RBC abnormalities at high dose. Greater incidence of ovarian cysts at high dose. Non-neoplastic finding: increase lipid deposition in liver, at high dose higher incidence, of dilated ovarian lumen, cystic endometrial glands and ovarian cysts. No evidence of carcinogenicity.
Rat, diet 104 weeks M 109 weeks F	4, 18, 80	Percent Survival Rates: 4 mg: Males 32; Females 22 18 mg: Males 22; Females 50 80 mg: Males 38; Females 42 Decreased weight gain at highest dose. Decreased food utlilization at low and high doses. Increased thyroxine levels in males. Decreased T 3 in high dose males, decreased thyroxine levels in high dose females. Decreased heart and kidney weights in males nondose dependent. The incidence of the following lesions were comparable to the incidence occurring in historical controls: mid dose male 1/50 renal lipoma, high dose male 3/50 and female 1/50 renal liposarcoma

Mutagencity:

Ames Test	Negative
Mouse Lymphoma Test	Negative
Chromosomal Aberration	Negative
Test Unscheduled DNA Synthesis	Negative
Micronucleus Test	Negative

Reproduction and Teratology:

Species/Route	Dosage mg/kg/day	Signs of Toxicity
Rat p.o. Reproductive Function and Fertility (Segment I)	4, 20, 100	FO: Dose dependent lethargy, slightly decreased weight gain in males at 20 and 100 mg before pairing, variable weight gain after pairing. Irregular estrous and increased pre-coital interval at high dose. Liver lesions at high dose in 2 females. . FI: non-dose dependent variations in growth during gestation and lactation in females. Reduced activity scores in males at 100 mg. Increased swimming times in females at 100 mg.
Rat p.o. Teratology (Segment II)	4, 20, 100	Mortality: 3 females died and 2 females sacrificed at high dose. Lethargy, ataxia and piloerection. Transient decreased weight gain. Decreased fetal weight at high dose. Early resorptions and post-implantation loss increased in treated and control animals. Necropsy: At 20 mg four fetuses exhibited abnormalities of soft and skeletal tissue. At high dose slightly increased change associated with: weight

Species/Route	Dosage mg/kg/day	Signs of Toxicity
		reduction involved brain, soft tissue arrangement and skeletal ossification, darkened adrenal medulla. Gross Visceral Observations: External Observation- Changes mostly comparable to historical control means except for small fetus size in high dose. Internal Observations - Changes comparable to historical control means or to study control. Skeletal Observations - Changes comparable to historical control means or study controls except for slight reductions in degree of ossification of cranial bones, sternebrae, and caudal vertebrae at high dose; these were considered to be associated with reduced fetal weight.
Rabbit p.o. Teratology (Segment II)	1, 4, 16	Sedation, transient decreased weight gain. Increased Pre-implantation loss at low dose and post-implantation loss at high dose. Changes included 3 small fetuses at mid dose, increased absent sternebrae at high dose and increased incomplete ossification at low and mid doses.

Species/Route	Dosage mg/kg/day	Signs of Toxicity
Rat p.o. Peri and Post-natal Development (Segment III)	4, 20, 100	Dose dependent lethargy, unsteadiness and ataxia. Gasping and impairment of righting reflex at mid and high dose. Decreased weight gain and 2 mortalities in high dose. At high dose, litters exhibited much reduced pre- and post-natal survival, mean litter size during lactation and birth weight of off-spring, extensive cannibalization and maternally inflicted injury.
Rat p.o. Milk production		Zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base / kg or 6 times the recommended human dose in mg / m2.

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