license no.024677

STILNOX CR Tablet 6.25 mg

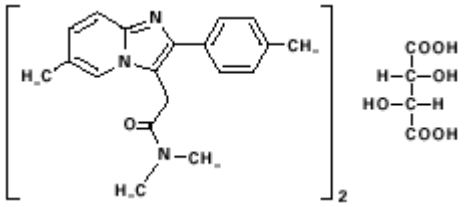
(zolpidem tartrate)

Complex sleep behavior (e.g. sleepwalking, sleepdriving, or activities during sleep or in dreaming state) may occur after the application of STILNOX CR. Some of the events may lead to severe injuries including death. If any patient developed complex sleep behavior after taking STILNOX CR, he or she must return to the clinic as soon as possible and discontinue the medication promptly.

DESCRIPTION AND COMPOSITION

STILNOX CR tablets contain zolpidem tartrate, which is a non-benzodiazepine hypnotic of the imidazopyridine class. STILNOX CR (zolpidem tartrate extended release tablets) is available in 6.25 mg strength tablets for oral administration.

Chemically, zolpidem tartrate is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

STILNOX CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The 6.25 mg STILNOX CR tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant 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) receptor.

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines,

pyrazolopyrimidines, or other drugs with known hypnotic properties. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ1 receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. The BZ_1 receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (parsreticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics
STILNOX CR exhibits biphasic absorption characteristics, which results in rapid release and initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond three hours after administration.
In adult and elderly patients treated with STILNOX CR, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

Absorption
Following administration of STILNOX CR, administered as a single dose in healthy male adult subjects, the mean peak concentration (C_{max}) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/ml) occurring at a median time (T_{max}) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).
A food-effect study in 45 healthy subjects compared the pharmacokinetics of STILNOX CR when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 23% and 30%, respectively, while median T_{max} was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, STILNOX CR should not be administered with or immediately after a meal.

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

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

Elimination
When STILNOX CR was administered as a single dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

Special Populations

Elderly

In 24 elderly (≥ 65 years) healthy subjects administered a single 6.25 mg dose of STILNOX CR, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (T_{max}) of 2 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

Hepatic Impairment

STILNOX CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

STILNOX CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate release formulation of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean ClCr = 6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. 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 for 14 or 21 days, 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, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing for 14 or 21 days, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients

with compromised renal function. As a general precaution, these patients should be closely monitored.

Controlled Trials Supporting Safety and Efficacy

STILNOX CR was evaluated in two placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

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

In this study, in patients treated with STILNOX CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs

Next-day Residual Effects

In two controlled clinical studies in the elderly (≥ 65 years of age) administered STILNOX CR 6.25 mg, the effect of STILNOX CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with STILNOX CR 6.25 mg using self-ratings of sedation.

Next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg STILNOX CR versus 5% of the placebo group (see ADVERSE REACTIONS). If the dose was increased, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg STILNOX CR versus 2% of the placebo group.

Rebound Effects

Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of STILNOX

CR. On the second night, there was no worsening compared to baseline in the STILNOX CR group.

INDICATIONS AND USAGE

Short-term treatment of insomnia in adults

[DESCRIPTION]
STILNOX CR (zolpidem tartrate extended release tablets) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset) (see CLINICAL PHARMACOLOGY: Controlled Trials Supporting Safety and Efficacy).
The clinical trials performed in support of efficacy were both 3 weeks in duration, although the final formal assessments of sleep latency and maintenance were performed after 2 weeks of treatment.

DOSAGE AND ADMINISTRATION

Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. The total dose should not exceed 12.5 mg per day.

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

STILNOX CR extended release tablets should be taken just before going to bed, or in bed.

As with all hypnotics, long-term use of zolpidem is not recommended. Treatment should be as short as possible and should not exceed four weeks. Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment (see PRECAUTIONS).

SPECIAL POPULATIONS

Children

Safety and effectiveness of zolpidem in patients under the age of 18 years have not been established. Therefore, zolpidem should not be prescribed in this population.

Elderly or debilitated subjects

Since elderly or debilitated patients may be especially sensitive to zolpidem, in these patients a 6.25 mg daily dose is recommended. The dose of STILNOX CR should be individualized.

Hepatic Impairment
As clearance and metabolism of zolpidem is reduced in hepatic impairment caution should be exercised in these patients, dosage should begin at 6.25 mg in subjects with hepatic impairment with particular caution being exercised in elderly patients.

CONTRAINDICATIONS

Zolpidem is contraindicated in patients with

- **a hypersensitivity to zolpidem or any of the inactive ingredients**
- **severe hepatic insufficiency**
- **acute and/or severe respiratory insufficiency**
- **sleep apnea syndrome**
- **myasthenia gravis**
- **patients developed complex sleep behavior after taking STILNOX CR (e.g. sleepwalking, sleepdriving, or activities during sleep or in dreaming state).**

WARNINGS

Zolpidem should be used with caution in patients with sleep apnea syndrome, and myasthenia gravis.

- **Respiratory Insufficiency**

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zolpidem is prescribed to patients with compromised respiratory function.

- **Risks from Concomitant Use with Opioids**

Concomitant use of opioids with benzodiazepines or other sedative-hypnotic drugs, including zolpidem, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zolpidem concomitantly with opioids, try to reduce the dosage and durations of concomitant use as much as possible, and follow patients closely for signs and symptoms of respiratory depression and sedation (see DRUG INTERACTIONS).

- **Hepatic Insufficiency**

Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and ADVERSE REACTIONS).

The product should be taken in a single intake and not be readministered during the same night.

Patients should be cautioned against engaging in hazardous activities such as driving a motor vehicle or operating machinery after taking STILNOX CR in order to avoid danger, and there may be a possible risk of drowsiness the morning after therapy. Sleep 7 to 8 hours after taking STILNOX CR is needed.

PRECAUTIONS

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 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

- **Pediatric Patients**

Safety and effectiveness of zolpidem have not been established in patients below the age of 18 years. **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: Special Populations: Children).

- **Elderly**

(see DOSAGE AND ADMINISTRATION)

- **Psychotic Illness**

Hypnotics such as zolpidem are not recommended for the primary treatment of psychotic illness.

- **Amnesia**

Anterograde amnesia may occur during the hours of following administration. In order to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

- **Suicidality and depression**

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including zolpidem. A causal relationship has not been established.
Zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present in such patients; therefore the least amount of zolpidem that is feasible should be supplied to these patients to avoid the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

- **Other Psychiatric and "Paradoxical" Reactions**

Other psychiatric and paradoxical reactions like restlessness, insomnia exacerbated, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behavior, delirium and other adverse behavioral effects are known to **occur when using** sedative/hypnotic agents like **zolpidem.** Should this occur, use of zolpidem should be discontinued.

These reactions are more likely to occur in the elderly.

- **Somnambulism and Associated Behaviors**

During the application of the drug containing zolpidem, recipients may develop complex sleep behavior (e.g. sleepwalking, sleepdriving, or activities during sleep or in dreaming state) and result in severe injuries (including inflicting on others or death, etc.) And such consequences won't be remembered by most of the patients after awaken. According to the post-marketing report, even under the recommended dose, recipients may develop complex sleep behavior regardless of concomitant use of alcohol or other central nervous system inhibitors (e.g. sedations, opioids, antianxiety agents). In the event of such situation, patients must return to the clinic as soon as possible and discontinue the medication promptly.

- **Psychomotor Impairment**

Like other sedative/hypnotic drugs, zolpidem has CNS-depressant effects.
The risk of psychomotor impairment, including impaired driving ability, is increased if:
zolpidem is taken within less than 7-8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zolpidem is co-administered with other CNS-depressants, alcohol, or with other

drugs that increase the blood levels of zolpidem (see DRUG INTERACTIONS, and EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINES).

- **Tolerance**

Some loss of efficacy to the hypnotic effects of sedative/hypnotic agents like zolpidem may develop after repeated use for a few weeks.

- **Dependence**

Use of zolpidem may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. Cases of dependence have been reported more frequently in patients treated with STILNOX CR for longer than 4 weeks. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. STILNOX CR should be used with extreme caution in patients with current or a history of alcohol or drug abuse.
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

- **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.
In the case of sedative/hypnotic agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval.

Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder.

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

STILNOX CR, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, STILNOX CR 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 in order to avoid danger, including potential impairment of the performance of such activities that may occur the day following ingestion of STILNOX CR.

- **Severe Injuries**

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

- **Patients with Long QT syndrome**

An *in vitro* cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells zolpidem may reduce the hERG related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

- **Severe Anaphylactic and Anaphylactoid Reactions**

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including STILNOX CR. 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 STILNOX CR should not be rechallenged with the drug.

General

Use in the Elderly and/or Debilitated Patients

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, special caution should be exercised. A lower dose of STILNOX CR is recommended in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

Use in Patients with Concomitant Illness

Clinical experience with zolpidem in patients with concomitant systemic illness is limited. Caution is advisable in using STILNOX CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem tartrate in

normal subjects or in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem tartrate immediate release tablets (10 mg) when compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if STILNOX CR is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate immediate release tablets, most of whom had pre-existing respiratory impairment, have been reported.
Data in end-stage renal failure patients repeatedly treated with zolpidem tartrate immediate release tablets did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see Pharmacokinetics).
A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with a lower dose in patients with hepatic compromise, and they should be closely monitored.

Information for Patients
Patient information is printed at the end of this insert. To assure safe and effective use of STILNOX CR, this information and instructions provided in the patient information section should be discussed with patients.

Laboratory Tests
There are no specific laboratory tests recommended.

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. Impaired alertness may make it dangerous to drive or operate machines.

- **CNS Depressants**

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability. In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

Zolpidem tartrate immediate release tablets were evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem tartrate produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

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

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

Since the systematic evaluations of STILNOX CR in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

- **Opioids**

The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zolpidem, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. If a decision is made to prescribe zolpidem concomitantly with opioids, try to reduce the dosage and durations of concomitant use as much as possible, and follow patients closely for signs and symptoms of respiratory depression and sedation (see WARNINGS).

- **CYP450 Inhibitors and Inducers**

Compounds that inhibit cytochrome P450 may enhance the activity of some hypnotics like zolpidem. Zolpidem is metabolized via hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4, CYP2C9 and CYP1A2. The pharmacodynamic effect of zolpidem is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St John's Wort. St. John's Wort has been shown to have a pharmacokinetic interaction with zolpidem. Mean C_{max} and AUC were decreased (33.7 and 30.0% lower, respectively) for zolpidem administered with St. John's Wort compared to zolpidem administered alone. Co-administration of St. John's Wort may decrease blood levels of zolpidem, concurrent use is not recommended.

Concurrent use of zolpidem with ketoconazole may enhance the sedative effects. Lower dose of zolpidem should be considered to use when co-administration with ketoconazole.

Drugs that Affect Drug Metabolism via Cytochrome P450:
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 tartrate immediate release tablets (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0»\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

The pharmacodynamic effect of zolpidem is decreased when it is administered with rifampicin (a CYP3A4 inducer).
A randomized, placebo-controlled, crossover interaction study in eight healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem tartrate immediate release tablets (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

- **Other Drugs**

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. The sedative and hypnotic effects of zolpidem were 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. However, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis:

Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley rats for two years at dietary dosages of 4, 18, and 80 mg/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day (40 and 80 times the maximum recommended human dose [MHRD] of STILNOX CR 12.5 mg [10 mg zolpidem base], respectively, on a mg/m^2 basis).

Mutagenesis:

Zolpidem did not have mutagenic activity in several tests including an in vitro bacterial reverse mutation (Ames) assay, an in vitro mammalian gene forward mutation assay in mouse lymphoma cells, and an in vitro unscheduled DNA synthesis in rat hepatocytes. Zolpidem was not clastogenic in an in vitro chromosomal aberration assay in human lymphocytes or in an in vivo micronucleus test in mice.

Impairment of Fertility:

Zolpidem tartrate was administered by oral gavage to Sprague-Dawley rats at doses of 4, 20, or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on postpartum day 25. Zolpidem administered at 100 mg base/kg/day was associated with irregular estrus cycles and prolonged pre-coital intervals, but did not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day (40 times the MRHD of STILNOX CR 6.25 mg on a mg/m^2 basis).

Pregnancy

The use of zolpidem is not recommended during pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zolpidem crosses the placenta.

A large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines during the first trimester of pregnancy. However, in certain epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

Administration of zolpidem during the late phase of pregnancy or during labor has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties (which may result in poor weight gain), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Moreover, infants born to mothers who took sedative/hypnotic agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the post-natal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If STILNOX CR is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

Teratogenic Effects: Pregnancy Category C.

Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg base/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg/day and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for

maternal and embryo/fetal toxicity was 4 mg base/kg/day (8 times the maximum recommended human dose [MRHD] of STILNOX CR 6.25 mg on a mg/m^2 basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (up to 30 times the MRHD of STILNOX CR 12.5 mg, on a mg/m^2 basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternebrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was below 1 mg base/kg/day (< 4-times the MRHD of STILNOX CR 6.25 mg, on a mg/m^2 basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day (16 times the MRHD of STILNOX CR 6.25 mg on a mg/m^2 basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg/day and higher. Decreased maternal body weight gain as well as evidence on non-secreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg/day. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg/day and higher and decreased pup survival at maternal doses of 100 mg base/kg/day. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg/day (8 times the MRHD of STILNOX CR 6.25 mg on a mg/m^2 basis).

Labor and Delivery:
STILNOX CR has no established use in labor and delivery (see Pregnancy).

Nursing Mothers
Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal subjects (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.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg.

The use of STILNOX CR in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

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

EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINES

Driving or operating machine should be avoided after using STILNOX CR in order to minimize this risk. There may be a possible risk of drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision and reduced alertness and impaired driving the morning after therapy. Sleep 7 to 8 hours after taking the drug is needed.

Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such effects. Patients should be advised not to use alcohol or other psychoactive substances when taking zolpidem.

The following adverse events include adverse events occurred in the pre-marketing and post-marketing periods:

ADVERSE REACTIONS

Associated with Discontinuation of Treatment:
In clinical trials with STILNOX CR, 3.5% of 201 patients receiving STILNOX CR discontinued treatment because of an adverse event. Events most commonly associated with discontinuation were somnolence (1.0%) and dizziness (1.0%).

Data from a double-blind study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem tartrate immediate releasing tablets revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Incidence in Controlled Clinical Trials:
Most Commonly Observed Adverse Events in Controlled Clinical Trials:

During treatment with STILNOX CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of STILNOX CR were headache, somnolence, and dizziness.

Adverse Reactions Observed at an Incidence of ≥1% in Controlled Clinical Trials:
The following tables enumerate treatment-emergent adverse reaction frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received STILNOX CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis of reference for estimating the relevance of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from results of two placebo-controlled efficacy trials involving STILNOX CR. These trials involved patients with primary insomnia who were treated for 3 weeks with STILNOX CR at dose of 6.25 mg (Table 1). The table includes only adverse reactions occurring at an incidence of at least 1% for STILNOX CR patients and with an incidence greater than that seen in the placebo patients.

Table 1: Incidences of Treatment-Emergent Adverse Events in a 3-Week Placebo-Controlled Clinical Trial in Elderly (Percentage of Patients Reporting)

Body System/ Adverse Reaction*	STILNOX CR 6.25 mg (N = 99)	Placebo (N = 106)
Infections and infestations		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0

Depressed mood	1	0
Nervous system disorders		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders**	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		
Flatulence	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system and breast disorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

* Events reported by at least 1% of patients treated with STILNOX CR and at greater frequency than in the placebo group.

** Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Dose Relationship for Adverse Reactions:
There is evidence suggesting a dose relationship for the adverse reactions associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Other Adverse Events Observed During the Premarketing Evaluation of STILNOX CR:
Other treatment-emergent adverse events associated with participation in STILNOX CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate release zolpidem tartrate.

Adverse Events Observed During the Premarketing Evaluation of Immediate Release Zolpidem Tartrate:
Immediate release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those were meaningless and those events were too minor. It is important to emphasize that, although the events reported did occur during treatment with immediate release zolpidem tartrate, they were not necessarily caused by it.

The following adverse events include adverse events occurred in the pre-marketing and post-marketing periods: 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.

Infections and infestations
Frequent: **influenza**
Infrequent: **gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection**

Immunologic System
Not known: **angioneurotic oedema**
Rare: **allergic reaction**

Psychiatric disorders
Frequent: **anxiety, psychomotor retardation, disorientation**
Infrequent: **restlessness, aggression, somnambulism (see PRECAUTIONS), depression, hallucination, including visual and hypnagogic hallucination, apathy, binge eating, confusional state, depersonalisation, depressed mood, disinhibition, euphoric mood, mood swings, nightmare, stress symptoms**
Rare: **libido disorder**
Very rare: **delusion, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)**
Not known: **anger, abnormal behaviour, complex sleep behavior (e.g. sleepwalking, sleepdriving, or activities during sleep or in dreaming state), delirium**

Nervous system disorders
Very frequent: headache, somnolence
Frequent: dizziness, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention
Infrequent: balance disorder, hypoaesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor
Rare: depressed level of consciousness, speech disorder

Eye disorders
Frequent: visual disturbance
Infrequent: eye redness, vision blurred, altered visual depth perception, asthenopia

Ear and labyrinth disorders
Infrequent: vertigo, tinnitus

Cardiac disorders
Infrequent: palpitations

Respiratory system
Infrequent: cough, dry throat, throat irritation
Very rare: respiratory depression (see WARNINGS)

Gastrointestinal system

Frequent: nausea, constipation
Infrequent: vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastrooesophageal reflux disease, abdominal pain

Liver and biliary system
Rare: hepatocellular, cholestatic or mixed liver injury (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS)

Skin and Appendages
Infrequent: rash, urticaria, dermatitis contact, skin wrinkling

Musculoskeletal system
Frequent: myalgia, muscle cramp, neck pain, back pain
Infrequent: arthralgia, muscular weakness

Urogenital system
Infrequent: dysuria

Reproductive system
Infrequent: dysmenorrhoea, menorrhagia, vulvovaginal dryness

Body as a whole
Frequent: fatigue
Infrequent: asthenia, chest discomfort, feeling drunk, influenza like illness, lethargy, pain, pyrexia
Rare: gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation) (see PRECAUTIONS)
Not known: drug tolerance

Investigations
Infrequent: blood pressure increased, body temperature increased, heart rate increased

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

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.

DRUG ABUSE AND DEPENDENCE

see PRECAUTIONS

Controlled Drugs:

According to Controlled Drugs Act, zolpidem tartrate is classified as the Schedule 4 controlled drug. Other Schedule 4 controlled drugs include benzodiazepines (diazepam, alprazolam, etc.) and non-benzodiazepine hypnotics (zaleplon and eszopiclone).

Abuse and Dependence:

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate immediate release tablets (STILNOX) 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

OVERDOSAGE

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. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other related 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. **Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions)**.

Zolpidem 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.

PACKAGING AND STORAGE
STILNOX CR 6.25 mg tablets are composed of two layers and are coated*, pink, round, bi-convex, debossed with ZMR on one side and supplied as 2-1000 tablets per bottle or carton.

* Layers are covered by the coating and are indistinguishable. The tablets are to be swallowed whole and should not be crushed, chewed, or divided.

Store below 30°C.

Manufacturer:

Sanofi Winthrop Industrie
30-36, Avenue Gustave Eiffel 37100 Tours, France.

License Holder:

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STCR-I2012-13