STILNOX® CR

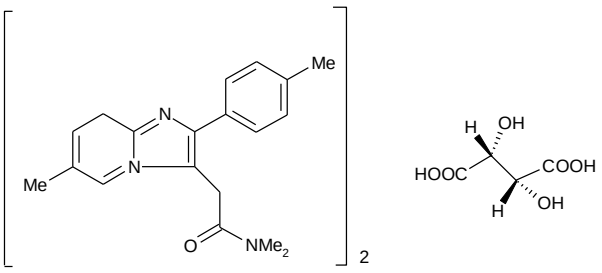
Zolpidem tartrate 6.25 mg

Zolpidem tartrate 12.5 mg

Modified-Release Tablets

[Sanofi logo]

DESCRIPTION



Zolpidem tartrate is a white to off white colourless, crystalline powder, sparingly soluble in water. Its chemical name is 2-(4-methylphenyl)-N,N,6-trimethylimidazo [1,2,a] pyridine-3-acetamide hemitartrate.
Its molecular formula is $(C_{19}H_{21}N_3O)_2$, $C_4H_6O_6$. MW is 764.9.

CAS numbers are 99294-93-6 (zolpidem tartrate) and 82626-48-0 (zolpidem).

Each tablet contains zolpidem tartrate 6.25 mg or 12.5 mg with lactose, microcrystalline cellulose, hypromellose, sodium starch glycollate type A, magnesium stearate, silica colloidal anhydrous, iron oxide yellow CI77492, iron oxide red CI77491, titanium dioxide, macrogol 3350, potassium acid tartrate and indigo carmine C173015.

PHARMACOLOGY

Pharmacodynamics

Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem i.e. the preservation of deep sleep (stage 3 and 4 slow wave sleep).

These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anti-convulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by the benzodiazepine antagonist flumazenil.

Pharmacokinetics:

The pharmacokinetic profile of STILNOX CR is characterised by rapid and almost complete absorption from the GI tract. STILNOX CR exhibits biphasic absorption characteristics, which result in rapid initial absorption and provide extended plasma concentrations beyond 3 hours after administration. Thereafter, the zolpidem plasma concentrations rapidly drops with a terminal half-life of 2.8 hours.

The absolute bioavailability is around 70% and the peak plasma concentration is reached at between 1.5and 2.5 hours. The interindividual variability (CV) is around 40-60% for AUC and 30-40% for C_{max}. The pharmacokinetics of zolpidem is linear within the therapeutic dosage. Administration after food decreases C_{max} and AUC by 30 and 23% and delays the time to maximal plasma concentrations by 2 hours.

The *in vitro* plasma protein binding is around 92%. The distribution volume in adults is 0.54 L/kg following intravenous administration.

The main cytochrome P450 enzyme involved in the hepatic biotransformation of zolpidem is CYP3A4. Other P40 isoenzymes such as CYP1A2, CYP2C9, CYP2C19 and CYP2D6 contribute minimally to the metabolism of zolpidem (see **Interactions**). Zolpidem itself is not a significant inhibitor or inducer of human CYP isoforms. All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). Furthermore, they do not interfere with zolpidem plasma binding. Clearance is around 212 mL/min. Reduced clearance of 100 mL/min has been noticed in elderly patients.

In adult and elderly patients who were treated for 3 weeks with STILNOX CR at 12.5 mg and 6.25 mg respectively, zolpidem plasma concentrations after wake-up (approximately 9 hours post-dose) were measured on day 1 and day 15. Zolpidem concentrations did not change upon repeated dosing, indicating no evidence of accumulation with STILNOX CR.

In the elderly, after a single dose of STILNOX CR 6.25 mg, maximal plasma concentration increased by 18 to 56% and the AUC by 7 to 82% as compared to young subjects after STILNOX CR 6.25 mg, without any change in the terminal half-life (around 3 hours). Therefore, the dose of STILNOX CR should be reduced by half in the elderly (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION).**

In patients with hepatic impairment, the clearance of zolpidem is decreased and the elimination half-life is extended (around 10 hours). In the case of liver cirrhosis a 5-fold increase of AUC and a 3-fold increase of half-life have been observed.

In patients with renal insufficiency, whether dialysed or not, there is a moderate increase (around 30%) of the volume of distribution compared to healthy subjects. Other pharmacokinetic parameters, such as clearance, AUC and elimination half-life are not affected. Therefore, no dose adjustment is necessary in patients with renal impairment.

Clinical trials

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).

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

Elderly outpatients (≥65 years) with primary insomnia (N=205) were evaluated in a doubleblind, 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 both studies, in patients treated with STILNOX CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

Next-day residual effects: The potential next-day residual effects associated with STILNOX CR were evaluated in 5 clinical studies; 3 controlled studies in adults (18-64 years) and 2 controlled studies in the elderly (≥65 years). In these studies using neurocognitive tests assessing vigilance, memory or motor function, no significant decrease in performance was observed with STILNOX CR, 8 hours after administration. In addition, no evidence of next-day residual effects were detected with zolpidem 12.5 mg and 6.25 mg using self-ratings of sedation.

Next day somnolence was reported by 15% of the adult patients who received 12.5 mg Stilnox CR versus 2% of the placebo group. Next day somnolence was reported by 6% of the elderly patients who received 6.25 mg Stilnox CR versus 5% of the placebo group.

Rebound Effects: In the two placebo-controlled 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.

Effects on Sleep Stages: In studies that measured the percentage of sleep time spent in each sleep stage, STILNOX CR has generally been shown to preserve sleep stages.

INDICATIONS

STILNOX CR is indicated for the short-term treatment of insomnia in adults (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Zolpidem is contraindicated in patients

- With a hypersensitivity to zolpidem or any of the inactive ingredients,
- With severe hepatic insufficiency,
- With acute and/or severe respiratory insufficiency,
- Who have previously experienced complex sleep behaviors after taking STILNOX CR.
- Who have myasthenia
- Who have sleep apnea syndrome

Due to lactose content, this medicinal product is contraindicated in the event of congenital galactosaemia, glucose or galactose malabsorption syndrome or lactase deficiency.

STILNOX CR should not be prescribed for children under 18 years of age.

WARNINGS AND 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 a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

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.

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.

As with other sedative/hypnotic drugs, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present, 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.

Risks from concomitant use with opioids:
Concomitant use of opioids with benzodiazepines and 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, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation.

Withdrawal, Rebound, Dependence and Tolerance
Tolerance
Continuous long-term use of STILNOX CR is not recommended and should not exceed four weeks.

Some loss of efficacy to the hypnotic effects of sedative/hypnotic agents 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. These patients should be under careful surveillance when receiving hypnotics.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations, delirium or epileptic seizures. Dependence has been very rarely reported with zolpidem.

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 minimising anxiety over such symptoms should they occur when the medicinal product is discontinued.

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

When STILNOX CR 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.

CNS effects

As with all patients taking CNS-depressant medications, patients receiving STILNOX CR should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from STILNOX CR therapy. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of STILNOX CR.

Use in the Elderly or Debilitated Patient

Elderly and debilitated patients may be particularly sensitive to the effects of STILNOX CR, therefore a 6.25 mg dose is recommended. This dose should not be exceeded in these patients. (See **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency

As clearance and metabolism of zolpidem is reduced in hepatic impairment, dosage should begin at 6.25 mg with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 12.5 mg only where the clinical response is inadequate and the drug is well tolerated. (See **Use In Elderly** and **DOSAGE AND ADMINISTRATION**).

Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy.

Renal Impairment

Dosage reduction is not necessary in patients with renal impairment, however, as a general precaution, these patients should be monitored closely (see **DOSAGE AND ADMINISTRATION**).

Depression, Psychosis and Schizophrenia

STILNOX CR is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary as depression may increase in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Pre-existing depression may be unmasked during the use of Stilnox CR. Suicidal tendencies may be present or uncovered and protective measures may be required. Intentional overdosage is more common in this group of patients: therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Psychotic illness

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

Amnesia

Sedative/hypnotic agents such as zolpidem may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

Other Psychiatric and Paradoxical Reactions

Other psychiatric and paradoxical reactions such as acute rage, restlessness, insomnia exacerbated, agitation, irritability, aggression, delusions, anger, nightmares, hallucinations**,** stimulation or excitement, abnormal behaviour, delirium and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like STILNOX CR. Should such reactions occur, STILNOX CR should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and Associated Behaviours
Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake, may occur following the first or any subsequent use of STILNOX CR. Patients can be seriously injured or injure others during complex sleep behaviors. Such injuries may be fatal. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Postmarketing reports have shown that complex sleep behaviors may occur with STILNOX CR alone at recommended doses, with or without the concomitant use of alcohol or other central nervous system (CNS) depressants (see Section 6). Discontinue STILNOX CR immediately if a patient experiences a complex sleep behaviour.

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

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

Chemical submission (Drug facilitated illicit use for criminal intent)

The rapid onset of sedation, coupled with the amnestic features of STILNOX CR, particularly when combined with alcohol, administered without knowledge of the victim, has proven to induce incapacitation and thus facilitate criminal actions (which could be dangerous). Healthcare Providers should prescribe STILNOX CR according to their clinical evaluation and only in case of medical need as it may be used illicitly for chemical submission.

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

Geriatric or Debilitated Patients
Such patients may be particularly susceptible to the sedative effects of the medication and associated giddiness, ataxias and confusion, which may increase the possibility of a fall.

Epilepsy
Abrupt withdrawal of CNS-depressant drugs in persons with convulsive disorders has been associated with a temporary increase in the frequency and or severity of seizures.

As with other sedative/hypnotics, caution is advised when STILNOX CR is used in these patients.

Abuse
Caution must be exercised in administering STILNOX CR to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

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.

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

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

Carcinogenicity, Mutagenicity, Impairment of Fertility

Mutagenic Potential

Zolpidem was not genotoxic in assays for gene mutations (*Salmonella typhimurium* histidine reversion assay, L5178Y mouse lymphoma assay), for chromosomal aberrations (human lymphocytes, mouse micronucleus assay) and for DNA repair assays (in human fibroblasts and rat hepatocytes). The mutagenic activity of zolpidem and/or its metabolites was equivocal in a Chinese hamster V79/HRPT gene mutation assay in the presence of metabolic activation.

Carcinogenic Potential

Two year dietary carcinogenicity studies on zolpidem were conducted in rats and mice. No evidence of carcinogenic potential was observed in mice at plasma concentrations (AUC) of zolpidem and its major human metabolite of about 2 and 7-12 times, respectively, the anticipated clinical exposure at the maximum recommended clinical dose. An increased incidence of renal liposarcomas was observed in male rats (6% cf. 0 in controls) at plasma concentrations (AUC) of zolpidem and its major metabolite of at least 22 and 9 times, respectively, the anticipated human exposure.

Pregnancy
The use of zolpidem is not recommended during pregnancy.

There is no evidence from extensive data collected during cohort studies in which patients were exposed to benzodiazepines in the first trimester of pregnancy that the drug has any malformative effects. However, in some epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines. According to these data, the incidence of cleft lip and palate would appear to be less than 2 per 1000 in neonates exposed to benzodiazepines in utero, compared to an expected ratio of 1 per 1000 in the general population.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of high benzodiazepine doses during the second and/or third trimester of pregnancy. Benzodiazepine treatment at the end of pregnancy, even at low doses, may cause signs of impregnation in the neonate, such as axial hypotonia and difficulty suckling, which gives rise to poor weight gain. These signs are reversible, but may last for 1 to 3 weeks depending on the half-life of the benzodiazepine prescribed. At high doses, respiratory depression or apnea and hypothermia may occur in the neonate. Furthermore, a neonatal withdrawal syndrome is possible, even if there are no signs of impregnation. This is

characterized in particular by overexcitability, agitation and tremor in the neonate, occurring some time after delivery. The time to onset depends on the elimination half-life of the medicinal product, and may be substantial if the elimination half-life is long.
Based on these data, as a precautionary measure, use of zolpidem should preferably be avoided during pregnancy, regardless of the trimester.
Women of child-bearing potential under zolpidem treatment should be instructed to contact their physician if they plan a pregnancy or if they are in the early stages of pregnancy, in order to reassess the need for treatment.
At term, if zolpidem treatment is absolutely necessary, high doses should be avoided and the effects described above taken into consideration during neonatal monitoring.

Lactation
Small quantities of zolpidem appear in breast milk. The use of zolpidem in nursing mothers is, therefore, not recommended.

Interactions with Other Drugs
CNS depressants
Co-administration of STILNOX CR with other CNS depressants should be exercised with caution since the central depressant effect may be additive. CNS depressants include alcohol, benzodiazepines, barbiturates, sedative/hypnotics, tricyclic antidepressants, MAOIs, antipsychotics, phenothiazines, skeletal muscle relaxants, antihistamines, neuroleptics, narcotic analgesics or anaesthetics. In the case of narcotic analgesics, enhancement of euphoria may also occur. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability

Alcohol
Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Alcohol potentiates the sedating effect of benzodiazepines and related substances. Impaired vigilance may prove dangerous when driving or using machines. Alcoholic drinks and medicinal products containing alcohol are to be avoided.

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. Limit dosage and duration of concomitant use of benzodiazepines and opioids

Imipramine
The sedative effects of imipramine 75 mg and zolpidem 20 mg were shown to be additive when the two compounds were given concomitantly in healthy volunteers. No pharmacokinetic interaction was shown between zolpidem and imipramine or its metabolite, desipramine.

Chlorpromazine
The combination of zolpidem 10 mg and chlorpromazine 50 mg in healthy volunteers produced an addition of effects seen in pyschometric tests and decreased alertness and psychomotor performance. No pharmacokinetic interaction was observed.

Haloperidol
No evidence of pharmacokinetic interaction between zolpidem 20 mg and haloperidol 2 mg was seen when they were given concurrently to healthy volunteers.

Caffeine
No change in the sleep inducing effect of zolpidem was seen when 300 mg caffeine was given in the evening 45 minutes before administration of zolpidem 20 mg to 8 healthy volunteers.

Warfarin

Prothrombin times were not prolonged in healthy adults when zolpidem 20 mg was administered for 4 consecutive nights concomitantly with warfarin. Warfarin had been given for at least 10 days previously to produce a 1.5 times prolongation of baseline prothrombin time in the volunteers. Zolpidem does not appear to modify the anticoagulant activity of warfarin.

Digoxin

The concurrent administration of zolpidem 10 mg once daily and digoxin 0.25 mg in healthy volunteers did not show any alteration of the pharmacokinetic or pharmacodynamic profile of digoxin.

H_2 - antagonists

Simultaneous administration of zolpidem 20 mg and cimetidine 200 mg tds and 400 mg at night or ranitidine 150 mg bd did not cause any significant change in psychometric tests from those produced by zolpidem alone. No change in the pharmacokinetics of zolpidem were caused by concomitant administration of either cimetidine or ranitidine.

Hepatic enzyme inhibitors and inducers

Zolpidem is metabolized via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2. Compounds which inhibit or enhance certain hepatic enzymes (particularly cytochrome P450) may increase or decrease the activity of some hypnotics. The pharmacodynamic effect of zolpidem is decreased when it is administered with rifampicin (a CYP3A4 inducer) and St John's Wort. St. Johns Wort has been shown to have a pharmacokinetic interaction with zolpidem**.** Mean Cmax 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**.** Ketoconazole has a significant but only quantitatively modest reduction in zolpidem clearance, with an increase in its pharmacodynamic effects. Patients should be advised that use of zolpidem with ketoconazole may enhance the sedative effects of zolpidem. However, when zolpidem is administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

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

ADVERSE REACTIONS

Clinical trials data

There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS events. These occur most frequently in elderly patients.

Associated with discontinuation of treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in US premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar European trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%) and nausea (0.6%).

In clinical trials with STILNOX CR, 3.5% of 201 patients receiving 6.25 mg or 12.5 mg of STILNOX CR discontinued treatment because of an adverse event. Events most commonly associated with discontinuation were somnolence (1.0%) and dizziness (1.0%).

Incidence in controlled clinical trials

Most commonly observed adverse events in controlled trials: During short-term treatment (up to 10 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 drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhoea (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%).

During longer-term treatment (3 weeks) with zolpidem at doses up to 12.5 mg, the most commonly observed adverse events associated with the use of zolpidem were headache (16%), somnolence (10 %) and dizziness (10%).

Adverse events observed at an incidence of ≥ 1% in controlled trials: The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received STILNOX in US placebo-controlled trials or modified-release STILNOX CR in placebo-controlled trials. Events reported by investigators were classified utilising a modified World Health Organisation (WHO) dictionary of preferred terms in STILNOX studies or MedDRA dictionary in modified-release STILNOX CR studies for the purpose of establishing event frequencies.

The following table was derived from a pool of 11 placebo-controlled short-term US 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 in Short-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	**STILNOX** (<10 mg) (N=685)	**Placebo** (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Nausea	2	3
Diarrhoea	1	-
Musculoskeletal System		
Myalgia	1	2

*Events reported by at least 1% of STILNOX patients are included.

The following table was derived from a pool of three placebo-controlled long-term efficacy trials involving STILNOX (zolpidem tartrate). 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 STILNOX patients.

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	**STILNOX** (<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	-
Fatigue	1	2
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	-
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhoea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7

Arthralgia	4	4
Respiratory System		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages	2	1
Rash		
Urogenital System		
Urinary tract infection	2	2

*Events reported by at least 1% of patients treated with STILNOX

The following table was derived from pooled results of two placebo-controlled efficacy trials involving modified-release zolpidem. These trials involved patients with primary insomnia who were treated for 3 weeks with modified-release zolpidem at doses of 6.25 or 12.5 mg. The table includes only adverse events occurring at an incidence of at least 1% for modified-release zolpidem patients.

Incidence of Treatment-Emergent Adverse Experiences in 3-week Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event *	**STILNOX CR** (≤12.5 mg (N=201)	**Placebo** (N=216)
Infections and infestations		
Nasopharyngitis	3	4
Influenza	2	0
Psychiatric disorders		
Anxiety	2	1
Psychomotor retardation	2	0
Disorientation	1	1
Nervous system disorders		
Headache	16	14
Somnolence	10	3
Dizziness	10	4
Memory disorders**	2	0
Disturbance in attention	1	1
Eye disorders		
Visual disturbance	1	0
Gastrointestinal System		
Nausea	6	5
Constipation	2	1
Abdominal pain upper	1	2
Musculoskeletal and connective tissue disorders		
Back pain	3	3
Myalgia	2	0
Muscle cramp	1	1
Neck pain	1	0
General disorders and administration site conditions		
Fatigue	3	2

* Events reported by at least 1% of patients treated with modified-release STILNOX CR.
** Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Adverse reactions of STILNOX

The following CIOMS frequency rating is used, when applicable:

Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥0.01 and <0.1%; very rare < 0.01%; Not known (cannot be estimated based on the available data). There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS events. As recommended in DOSAGE AND ADMINISTRATION, they should in theory, be less if zolpidem is taken immediately before retiring, or in bed.

They occur most frequently in elderly patients.

The adverse drug reactions reported in the zolpidem extended release tablets group with an incidence greater than in the placebo group in clinical trials are listed below.

Infections and infestations

Common = influenza

Uncommon = gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection

Immune system disorders

Not known = angioneurotic edema

Gastrointestinal

Common = diarrhoea, nausea, vomiting, abdominal pain, constipation

Uncommon = flatulence, frequent bowel movements, gastroesophageal reflux disease

Nervous system disorders

Very common = headache, somnolence

Common = dizziness, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention

Uncommon = balance disorder, hypoesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor

Rare = Ataxia, depressed level of consciousness, speech disorder

Eye disorders

Common = visual disturbance

Uncommon = Diplopia, eye redness, vision blurred, altered visual depth perception, Asthenopia

Ear and labyrinth disorders

Uncommon = vertigo, tinnitus

Cardiac disorders

Uncommon = palpitations

Psychiatric disorders

Common = anxiety, psychomotor retardation, disorientation

Uncommon = restlessness, aggression, somnambulism, depression, hallucination,

including visual and hypnagogic hallucination, apathy, binge eating, confusional state, depersonalization, 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 behaviors, delirium

Most of these psychiatric undesirable effects are related to paradoxical reactions.

Respiratory, thoracic and mediastinal disorders

Uncommon = cough, dry throat, throat irritation

Very Rare = respiratory depression

Hepatobiliary disorders

Rare = hepatocellular, cholestatic or mixed liver injury

Skin and subcutaneous tissue disorders

Uncommon = rash, pruritus, hyperhidrosis, urticaria, dermatitis contact, skin wrinkling

Metabolism and nutrition disorder

Uncommon = appetite disorder

Musculoskeletal and connective tissue disorders

Common = myalgia, muscle cramp, neck pain, back pain

Uncommon = arthralgia, muscular weakness

Renal and urinary disorders

Uncommon = dysuria

Reproductive system and breast disorders

Uncommon = dysmenorrhea, menorrhagia, vulvovaginal dryness

General disorders and administration site conditions

Common = fatigue

Uncommon = 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)

Not known = drug tolerance

Investigations

Uncommon = blood pressure increased, body temperature increased, heart rate increased

Injury, poisoning and procedural complications

Uncommon = contusion, neck injury

Surgical and medical procedures

Uncommon = tooth repair

Social circumstances

Uncommon = exposure to poisonous plant

Elevated liver enzymes, rash, pruritus, and urticaria have also been reported.

The treatment-emergent adverse events associated with participation in modified-release STILNOX CR studies were not different in nature or frequency to that seen in studies with STILNOX.

DOSAGE AND ADMINISTRATION

The treatment should always be implemented at the lowest effective dose, and the maximum dosage should never be exceeded.

STILNOX CR acts rapidly and should therefore be taken immediately before retiring. As with all hypnotics, long-term use is not recommended and a course of treatment should not exceed four weeks.

The effect of Stilnox CR may be slowed by ingestion with or immediately after a meal.
The lowest effective daily dose of zolpidem should be used and must not exceed 12.5 mg

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

Discontinuation of treatment: see **ADVERSE REACTION** section.

Withdrawal Effects: see **PRECAUTIONS**

Recommended Dosage:

Tablets should not be divided, crushed or chewed

Adults
The recommended daily dose is 12.5 mg.

Elderly or Debilitated Patients
The recommended daily dose is 6.25 mg

Hepatic Impairment
The recommended daily dose is 6.25 mg and these patients should be closely monitored. STILNOX CR should not be used in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

Renal impairment
No dosage adjustment is necessary in these patients, although they should be closely monitored.

Children
As the safety and efficacy of STILNOX CR has not yet been established, the use of STILNOX CR in children under 18 years of age is contra-indicated.

OVERDOSAGE

Signs and Symptoms: In reports of overdose with immediate-release zolpidem alone, impairment of consciousness has ranged from somnolescence to light coma. Individuals have totally recovered from zolpidem overdoses up to 400 mg, 40 times the recommended dose, however fatalities have occurred when overdoses of multi CNS depressants were taken. No differences were identified with reports of overdose with controlled release zolpidem.

Management: General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Sedative drugs should be withheld, even if excitation occurs.

Zolpidem has been shown in trials to be non-dialysable.

Use of flumazenil may be considered when serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms, such as convulsions, since zolpidem does not exhibit the anticonvulsant effects of benzodiazepines.

PRESENTATION

STILNOX CR 6.25 mg tablets are pink, bi-convex two-layer tablets engraved with ZMR on one side.

STILNOX CR 12.5 mg tablets are blue, bi-convex two-layer tablets engraved with ZMR on one side.

STILNOX CR 6.25 mg & 12.5 mg tablets are available in blister packs of 14 tablets.

STORAGE

Store below 30°C.

MANUFACTURER

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Revision date:
Oct 2023
(CCDS v18)