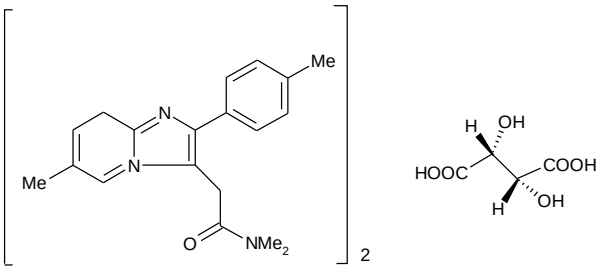
PRODUCT INFORMATION

STILNOX® CR MODIFIED RELEASE TABLETS

WARNING: Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

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 monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycollate type A, magnesium stearate, colloidal anhydrous silica, iron oxide yellow CI77492, iron oxide red CI77491, titanium dioxide, macrogol 3350, potassium hydrogen 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:

Absorption

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 concentration 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.

Distribution

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

Metabolism

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 WITH OTHER MEDICINES**). Zolpidem itself is not a significant inhibitor or inducer of human CYP isoforms.

Excretion

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.

Special Populations

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 modified-release 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 double-blind, randomised, parallel-group three-week trial comparing STILNOX CR 12.5 mg and

placebo. STILNOX CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep maintenance (by decreasing Wake time After Sleep Onset (WASO mean±SD) by 30±28 minutes during the first two nights and by 27±27 min after two weeks of treatment), sleep induction (by decreasing latency to persistent sleep (LPS mean±SD) by 23±28 min during the first two nights and by 20±28 min after two weeks of treatment) and sleep duration (by increasing total sleep time (TST mean±SD) by 58±46 min during the first two nights and by 41±52 min after two weeks of treatment), during the first two nights and after two weeks of treatment in adult and elderly patients respectively. STILNOX CR 12.5 mg was also superior to placebo on the patient-reported global impression regarding the aid to sleep, after the first two nights and after three weeks of treatment.
Elderly outpatients (≥65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomised, parallel-group, three-week trial comparing STILNOX CR 6.25 mg and placebo. STILNOX CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep maintenance (by decreasing WASO mean±SD by 32±26 min during the first two nights and by 18±31 min after two weeks of treatment), sleep induction (by decreasing LPS mean±SD by 17±21 min during the first two nights and by 15±25 min after two weeks of treatment) and sleep duration (by increasing TST mean±SD by 49±39 min during the first two nights and by 28±44 min after two weeks of treatment). STILNOX CR 6.25 mg was also superior to placebo on the patient's reported global impression regarding the aid to sleep, after the first two nights and after three weeks of treatment. The hypnotic efficacy and safety of STILNOX CR has not been assessed in children under 18 years of age and pregnant women.

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

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

- Sleep apnoea.
- Known hypersensitivity to zolpidem or other ingredients in the tablet.
- Myasthenia gravis.
- Severe hepatic insufficiency.
- Acute and**/**or severe pulmonary insufficiency.
- Prior or concomitant intake with alcohol.
- STILNOX CR should not be prescribed for children under 18 years of age.

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.

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 sedative/hypnotic agents may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or 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 or epileptic seizures. Dependence has been very rarely reported with zolpidem.

Rebound insomnia

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.

There are indications that, in the case of sedative/hypnotic agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

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.

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 test showed that under experimental conditions, using very high concentration and pluripotent stem cells, zolpidem may reduce the hERG related potassium currents. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

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 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. Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**).

Respiratory function

Both animal and human pharmacology studies performed with STILNOX CR have not observed any effect on the respiratory centre. However, as other sedative/hypnotics have the capacity to depress respiratory drive, caution is advised when STILNOX CR is administered to patients with respiratory insufficiency (See **CONTRAINDICATIONS**).

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 impairment

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 **PRECAUTIONS 'Use in the 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**).

Memory Impairment

Sedative/hypnotic agents 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.

Suicidality, Depression, Psychosis and Schizophrenia

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. 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.

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 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

Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of such behaviours, as does the use of STILNOX CR at doses exceeding the maximum recommended dose. Discontinuation of STILNOX CR should be strongly considered for patients who report such behaviours (for example, sleep driving), due to the risk to the patient and others (see **INTERACTIONS WITH OTHER MEDICINES** and **ADVERSE EFFECTS**). These events can occur in sedative-hypnotic naive as well as sedative-hypnotic experienced patients.

Psychomotor Impairment

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.

Interactions with Alcohol

Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**). Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance (see **PRECAUTIONS** '**Somnambulism and Associated Behaviours'** above).

Severe Anaphylactic and Anaphylactoid Reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported inpatients 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.

Effects on Ability to Drive and use Machinery

This preparation is to aid sleep. Patients should not drive or operate machinery for 8 hours after taking STILNOX CR.

Adverse effects including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, reduced alertness and/or impaired driving may continue the following day. In order to minimise this risk a full night of sleep (7-8h) is recommended. After ingesting the medicine, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor co-ordination such as operating machinery or driving a motor vehicle, including potential impairment of the performance of such activities that may occur the day following ingestion of STILNOX CR. 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.

Use in Pregnancy

Category B3

This drug has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is uncertain in humans. As a precautionary measure, it is preferable to avoid the use of zolpidem in pregnancy.

Teratogenic effects

In reproductive toxicity studies, rats treated with oral zolpidem with estimated exposures (AUC) to zolpidem and its major metabolite of 41 and 15 times, respectively, the anticipated clinical exposure did not exhibit teratogenic effects but post-implantation survival index and postpartum viability of the offspring were significantly reduced. In rats, delayed ossification of foetal skull bones occurred at zolpidem and metabolite exposure levels of 8 and 3 times, respectively, the anticipated clinical exposure.

Rabbits treated with oral zolpidem with estimated exposure to zolpidem of 0.6-2.6 times the anticipated clinical exposure did not exhibit teratogenic effects, but there was increased post-implantation loss.

Although animal studies have not shown any teratogenic effects with zolpidem, the safety of zolpidem in human pregnancy has not been established.

Non teratogenic effects

Cases of severe neonatal respiratory depression have been reported when zolpidem was used with other CNS depressants at the end of pregnancy.

Infants born to mothers who took hypnotics chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Use during Lactation

The use of STILNOX CR in nursing women is not recommended as small quantities of zolpidem are excreted into breast milk.

INTERACTIONS WITH OTHER MEDICINES

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, anxiolytics, tricyclic antidepressants, MAOIs, antipsychotics, phenothiazines, skeletal muscle relaxants, antihistamines, neuroleptics, antiepileptic drugs, narcotic analgesics or anaesthetics. 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.

Alcohol

Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**). Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of somnambulism and associated behaviours (see **PRECAUTIONS** '**Somnambulism and Associated Behaviours'**).

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 a CYP3A4 inducer such as rifampicin and St John's Wort. Co-administration of St John's Wort may decrease blood levels of zolpidem, therefore 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 EFFECTS

Clinical trials data

There is evidence of a dose-relationship for adverse effects associated with STILNOX CR 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.

STILNOX Post Marketing Data

Gastrointestinal		
Common	=	Nausea, constipation, diarrhoea
Uncommon	=	Vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastro-oesophageal reflux disease
Infections and infestations		
Common	=	Influenza
Uncommon	=	Gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection
Immune system		
	=	Angioneurotic oedema has been reported
Metabolism and nutrition disorders		
Uncommon	=	Appetite disorder
Neurological		
Very Common	=	Headache, somnolence
Common	=	Dizziness, memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention
Uncommon	=	Balance disorder, hypoaesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor
Rare	=	Dysarthria, depressed level of consciousness
Visual		
Common	=	Visual disturbance
Uncommon	=	Eye redness, vision blurred, altered visual depth perception, asthenopia
Rare	=	Diplopia
Psychiatric		
Common	=	Drowsiness, anxiety, psychomotor retardation, disorientation
Uncommon	=	Confusion, hallucinations, memory disturbances, reduced alertness, depression, apathy, binge eating, depersonalisation, depressed mood, disinhibition, euphoric mood, visual, hypnagogic hallucination, mood swings, nightmares, stress symptoms
Rare	=	Perceptual disturbances, restlessness, aggravated insomnia, libido disorder, agitation, irritability, aggressiveness, delusion, rages, inappropriate behaviour, somnambulism (see **PRECAUTIONS** – '**Somnambulism and Associated Behaviours**'), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), other adverse behavioural effects
		Anger and abnormal behaviour have been reported
Hepatobiliary		Hepatocellular, cholestatic and mixed liver injury has been reported.
disorders		
Skin and subcutaneous tissue		
Uncommon		Rash, urticaria, dermatitis contact, skin wrinkling
Rare	=	Angioneurotic oedema, hyperhydrosis
General disorders and administration site conditions		
Common	=	Fatigue
Uncommon	=	Asthenia, chest discomfort, feeling drunk, influenza like illness, lethargy, pain, pyrexia

Rare	=	Fall, gait disturbances, drug tolerance
Cardiac		
Uncommon	=	Palpitations
Respiratory, thoracic and mediastinal		
Uncommon	=	Cough, dry throat, throat irritation
	=	Respiratory depression (see **PRECAUTIONS** – **Respiratory function**) has been reported
Ear and labyrinth		
Uncommon	=	Vertigo, tinnitus
Musculoskeletal and connective tissue		
Common	=	Myalgia, muscle cramp, neck pain, back pain
Uncommon	=	Arthralgia
Rare	=	Muscular weakness
Renal and urinary		
Uncommon	=	Dysuria
Reproductive system and breast		
Uncommon	=	Dysmenorrhoea, menorrhagia, vulvovaginal dryness
Investigations		
Uncommon	=	Blood pressure increased, body temperature increased, heart rate increased

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

STILNOX CR acts rapidly and should therefore be taken immediately before retiring, or in bed. STILNOX CR should be taken in a single intake and not be re-administered during the same night. As with all hypnotics, long-term use of zolpidem is not recommended and a course of treatment should not exceed four weeks.

For oral use only.

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

Withdrawal Effects: see **PRECAUTIONS**

Recommended Dosage:

Tablets should not be divided, crushed or chewed

Adults

The recommended daily dose is 12.5 mg. The lowest effective daily dose of zolpidem should be used and not exceed 12.5mg.

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 or with other CNS depressant agents (including alcohol), impairment of consciousness has ranged from somnolescence to coma, and more severe symptomatology, including fatal outcomes have been reported. 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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 2 (sample), 7[#], 10[#], & 14, 20[#], 21[#], 28[#] and 100[#] tablets.

Store below 30ºC.

[#]Not Marketed

NAME AND ADDRESS OF SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park, NSW 2113

POSIONS SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG

6 July 2006

DATE OF MOST RECENT AMENDMENT

9 December 2016