AUSTRALIAN PRODUCT INFORMATION – STILNOX CR (ZOLPIDEM TARTRATE) 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.

1 NAME OF THE MEDICINE

Zolpidem tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains zolpidem tartrate 6.25 mg or 12.5 mg.

Zolpidem tartrate is a white to off white colourless, crystalline powder, sparingly soluble in water.

Excipients: 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.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

STILNOX CR is indicated for the short-term treatment of insomnia in adults (see Section 4.2 Dose and method of administration).

4.2 DOSE AND METHOD OF 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. Treatment should be as short as possible and should not exceed four weeks.

For oral use only.

Discontinuation of treatment: see Section 4.8 Adverse effects (Undesirable effects).

Withdrawal Effects: see Section 4.4 Special warnings and precautions for use.

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

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem. The recommended daily dose is 6.25 mg

Hepatic Impairment

As clearance and metabolism of zolpidem is reduced in hepatic impairment, caution should be exercised in these patients with particular caution being exercised in elderly patients. 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 Section 4.3 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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 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; it 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 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 Section 4.3 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 Section 4.3 Contraindications).

Use in 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 Section 4.4 Special warnings and precautions for use 'Use in the elderly' and Section 4.2 Dose and method of administration). Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy.

Use in renal impairment

Dosage reduction is not necessary in patients with renal impairment, however, as a general precaution, these patients should be monitored closely (see Section 4.2 Dose and method of administration).

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 Section 4.2 Dose and method of administration).

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.

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 should be administered with caution in patients exhibiting symptoms of depression. STILNOX CR is not recommended as primary therapy in patients with psychotic illness, including 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 Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse Effects (Undesirable effects)). These events can occur in sedative-hypnotic naive as well as sedative-hypnotic experienced patients.

Psychomotor Impairment

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.

Interactions with Alcohol

Prior or concomitant intake with alcohol is contraindicated (see Section 4.3 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 see Section 4.4 Special warnings and precautions for use 'Somnambulism and Associated Behaviours' above**).**

Risks from Concomitant use with Opiods

Concomitant use of sedative-hypnotic drugs, including zolpidem, with opioids may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and zolpidem 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. (see Section 4.5 Interactions with other medicines and other forms of interactions).

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.

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.

Paediatric use

See Section 4.2 Dose and method of administration

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, antidepressant agents (including tricyclic antidepressants, MAOIs), antipsychotics (neuroleptics), 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.

Opioids

The concomitant use of 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 zolpidem and opioids (see Section 4.4 Special warnings and precautions for use 'Risks from Concomitant use with Opioids').

Alcohol

Prior or concomitant intake with alcohol is contraindicated (see Section 4.3 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 Section 4.4 Special warnings and precautions for use '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 psychometric 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.

H2 - 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 like zolpidem. 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

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. The use of zolpidem is not recommended during pregnancy.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines or other sedative-hypnotic drugs such as zolpidem during 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, and respiratory depression.

If zolpidem 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

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. Appropriate monitoring of the newborn in the postnatal period is recommended.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 (7-8 hours) 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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		
Rash	2	1
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

Infections and infestations		
Common	=	Influenza
Uncommon	=	Gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper respiratory tract infection
Immune system disorders		
Rare	=	Angioneurotic oedema
Metabolism and nutrition disorders		
Uncommon	=	Appetite disorder
Psychiatric disorders		
Common	=	Drowsiness, anxiety, psychomotor retardation, disorientation
Uncommon	=	Confusion, restlessness, aggressiveness, somnambulism (see Section 4.4 – Special warnings and precautions for use 'Somnambulism and Associated Behaviours'), hallucinations (including visual and hypnagogic hallucinations), memory disturbances, reduced alertness, depression, apathy, binge eating, depersonalisation, depressed mood, disinhibition, euphoric mood, mood swings, nightmares, stress symptoms
Rare	=	Perceptual disturbances, aggravated insomnia, libido disorder, agitation, irritability, delusion, rages, inappropriate behaviour, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), other adverse behavioural effects
	=	Anger and abnormal behaviour
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, hypoaesthesia, paraesthesia, ataxia, burning sensation, dizziness postural, dysgeusia, muscle contractions involuntary, tremor
Rare	=	Speech disorder (dysarthria), depressed level of consciousness
Eye disorders		
Common	=	Visual disturbance
Uncommon	=	Eye redness, vision blurred, altered visual depth perception, asthenopia
Rare	=	Diplopia
Ear and labyrinth disorders		
Uncommon	=	Vertigo, tinnitus
Cardiac disorders		
Uncommon	=	Palpitations
Respiratory, thoracic and mediastinal disorders		
Uncommon	=	Cough, dry throat, throat irritation
	=	Respiratory depression (see Section 4.4 Special warnings and precautions for use – Respiratory function) has been reported

Gastrointestinal disorders		
Common	=	Nausea, constipation, diarrhoea
Uncommon	=	Vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastro-oesophageal reflux disease
Hepatobiliary disorders		
Rare	=	Hepatocellular, cholestatic and mixed liver injury
Skin and subcutaneous tissue		
Uncommon	=	Rash, urticaria, dermatitis contact, skin wrinkling, hyperhydrosis
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	=	Dysmenorrhoea, menorrhagia, vulvovaginal dryness
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
Investigations		
Uncommon	=	Blood pressure increased, body temperature increased, heart rate increased
Injury, poisoning and procedural complications		
Uncommon	=	Contusion, neck injury

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

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.

5.2 PHARMACOKINETIC PROPERTIES

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 1.5 and 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 Section 4.5 Interactions with other medicines and other forms of interactions). 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 Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

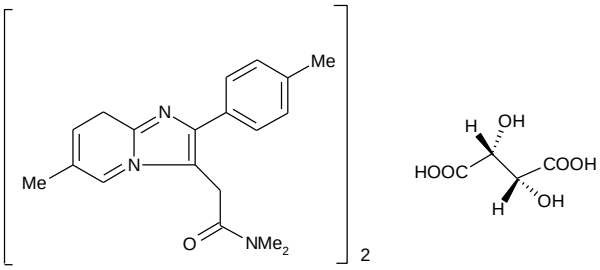
[#]Not Marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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 number

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4)

8 SPONSOR

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Tel: 1800 818 806
Email: ae@sanofi.com

9 DATE OF FIRST APPROVAL

6 July 2006

10 DATE OF REVISION

10 May 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Safety statement added of "Treatment should be as short as possible"
4.4	Additional statements added about dependence
4.8	Hyperhydrosis upgraded to uncommon.
8	Telephone number and email address added