AUSTRALIAN PRODUCT INFORMATION
BELSOMRA® (suvorexant)

1 NAME OF THE MEDICINE

suvorexant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BELSOMRA tablets contain the active ingredient suvorexant.

BELSOMRA is available for oral use as film-coated tablets containing 15 or 20 mg of suvorexant.

List of excipients with known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

BELSOMRA (suvorexant) 15 mg: is a white, oval, biconvex, film coated tablet, marked with "✪" on one side and 325 on the other side.

BELSOMRA (suvorexant) 20 mg: is a white, round, biconvex, film coated tablet, marked with "✪" and 335 on one side, and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BELSOMRA is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Following initiation of treatment, continuation should be re-evaluated after 3 months [see Section 5.1 Pharmacodynamic Properties, Clinical trials and Section 4.8 Adverse Effects (Undesirable Effects) for clinical trial durations].

4.2 DOSE AND METHOD OF ADMINISTRATION

BELSOMRA may be taken with or without food.

BELSOMRA should be taken no more than once per night and within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening.

For dosage in non-elderly adults (<65years) and elderly adults (≥65 years):

The recommended dose is 20 mg for non-elderly adults and 15 mg for elderly adults.

This dose should not be exceeded. Higher doses (30 mg and 40 mg) were found to have similar efficacy to lower doses (15 mg and 20 mg) but significantly more adverse effects were reported at the higher doses [see Section 5.1 Pharmacodynamic Properties, Clinical trials and Section 4.8 Adverse Effects (Undesirable Effects)].

For use with strong or moderate CYP3A inhibitors:

BELSOMRA is not recommended for patients taking concomitant strong or moderate CYP3A inhibitors as the exposure to suvorexant is increased.

Patients with hepatic impairment

Suvorexant pharmacokinetics were similar in patients with moderate hepatic impairment and healthy subjects. BELSOMRA has not been studied in patients with severe hepatic impairment and is not recommended for these patients [see Section 4.4 Special Warnings and Precautions for Use, Use in hepatic impairment and Section 5.2 Pharmacokinetic Properties].

Patients with renal impairment

Suvorexant pharmacokinetics were similar in patients with severe renal impairment and healthy subjects [see Section 5.2 Pharmacokinetic Properties].

4.3 CONTRAINDICATIONS

BELSOMRA is contraindicated in patients with known hypersensitivity to suvorexant or any of its inactive ingredients.

BELSOMRA is contraindicated in patients with narcolepsy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CNS Depressant Effects

BELSOMRA is a central nervous system (CNS) depressant that can impair daytime wakefulness even when used as prescribed. Prescribers should monitor for somnolence and CNS depressant effects, but impairment can occur in the absence of symptoms, and may not be reliably detected by ordinary clinical exam (i.e., less than formal testing of daytime wakefulness and/or psychomotor performance). CNS depressant effects may persist in some patients for up to several days after discontinuing BELSOMRA.

BELSOMRA can impair driving skills and may increase the risk of falling asleep while driving. Discontinue in patients who drive if daytime somnolence develops. In a study of healthy adults, driving ability was impaired in some individuals taking 20 mg BELSOMRA [see Section 4.8 Adverse Effects (Undesirable Effects), Studies pertinent to safety for hypnotic medicines]. Although pharmacodynamic tolerance or adaptation to some adverse depressant effects of BELSOMRA may develop with daily use, patients using the 20 mg dose of BELSOMRA should be cautioned against next-day driving and other activities requiring full mental alertness.

Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Patients should be advised not to consume alcohol in combination with BELSOMRA because of additive effects [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions]. The use of BELSOMRA with other drugs to treat insomnia is not recommended [see Section 4.2 Dose and Method of Administration].

The risk of next-day impairment, including impaired driving, is increased if BELSOMRA is taken with less than a full night of sleep remaining, if a higher than the recommended dose is taken, if co-administered with other CNS depressants, or if co-administered with other drugs that increase blood levels of BELSOMRA. Patients should be cautioned against driving and other activities requiring complete mental alertness if BELSOMRA is taken in these circumstances.

Need to evaluate for co-morbid diagnoses

The effect of BELSOMRA has been assessed in patients with primary insomnia in clinical trials. Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. Worsening of insomnia or the emergence of new cognitive or

behavioural abnormalities may be the result of an unrecognised underlying psychiatric or physical disorder other than insomnia. Such findings have emerged during the course of treatment with hypnotic medicines. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.

Abnormal thinking and behavioural changes

A variety of cognitive and behavioural changes have been reported to occur in association with the use of hypnotics such as BELSOMRA. Complex behaviours such as "sleep-driving" (i.e., driving while not fully awake after ingestion of an hypnotic) and other complex behaviours (e.g., sleep walking, preparing and eating food), with amnesia for the event, have been reported in association with the use of hypnotics. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. The use of alcohol and other CNS depressants may increase the risk of such behaviours.

Discontinuation of BELSOMRA should be strongly considered for patients who report any complex sleep behaviour due to the risks to patient and others [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, CNS-active agents].

Worsening of depression/suicidal ideation

In clinical studies, a dose-dependent increase in suicidal ideation was observed in patients taking BELSOMRA as assessed by questionnaire. Immediately evaluate patients with suicidal ideation or any new behavioural sign or symptom.

In primarily depressed patients treated with sedative hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

The emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Patients with compromised respiratory function

BELSOMRA has not been studied in patients with severe Obstructive Sleep Apnoea (OSA) or severe Chronic Obstructive Pulmonary Disease (COPD). Caution is advised if BELSOMRA is prescribed to patients with compromised respiratory function. [See Section 4.8 Adverse Effects (Undesirable Effects), Studies pertinent to safety concerns for hypnotic medicines.]

Sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy-like symptoms

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions by the patient, can occur with the use of BELSOMRA. Prescribers should explain the nature of these events to patients when prescribing BELSOMRA.

Symptoms similar to mild cataplexy can occur, with risk increasing with the dose of BELSOMRA. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur both at night and during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise).

Abuse

Abuse of BELSOMRA poses an increased risk of somnolence, daytime sleepiness, impaired reaction time and impaired driving skills. Patients at risk for abuse may include those with

prolonged use of BELSOMRA, those with a history of drug abuse, and those who use BELSOMRA in combination with alcohol or other abused drugs.

For use with strong and moderate CYP3A inhibitors

Concomitant use of BELSOMRA with strong or moderate CYP3A inhibitors is not recommended [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects of other medicines on suvorexant].

Use in hepatic impairment

BELSOMRA has not been studied in patients with severe hepatic impairment and is not recommended for these patients [see Section 4.2 Dose and Method of Administration, Patients with hepatic impairment].

Use in the elderly

Of the total number of patients treated with BELSOMRA (N=1784) in phase 3 clinical safety and efficacy studies, 829 patients were 65 years and over, while 159 patients were 75 years and over. No clinically meaningful differences in safety or effectiveness were observed between these patients and younger patients at the recommended doses. However, greater sensitivity of some older individuals cannot be ruled out [see Section 4.2 Dose and Method of Administration, Elderly adults (≥ 65 yrs), Section 5.1 Pharmacodynamic Properties, Clinical trials and Section 5.2 Pharmacokinetic Properties].

Paediatric use

Safety and effectiveness of BELSOMRA in paediatric patients have not been established. Therefore, BELSOMRA should not be used in children.

Effect on laboratory tests

In the pooled data from the three placebo-controlled studies in patients with insomnia, no clinically meaningful differences were observed between patients receiving BELSOMRA and those receiving placebo in routine serum chemistry, haematology, or urinalysis parameters.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CNS-active agents

When BELSOMRA was co-administered with alcohol, additive psychomotor impairment was demonstrated. There was no alteration in the pharmacokinetics of either medicine [see Section 4.4 Special Warnings and Precautions for Use, Abnormal thinking and behavioural changes, CNS depressant effects and Section 5.2 Pharmacokinetic Properties].

When BELSOMRA was co-administered with paroxetine, no clinically significant pharmacokinetic or pharmacodynamic interaction was demonstrated [see Section 4.4 Special Warnings and Precautions for Use, Abnormal thinking and behavioural changes, CNS depressant effects and Section 5.2 Pharmacokinetic Properties].

Effects of other medicines on BELSOMRA
Metabolism by CYP3A is the major elimination pathway for suvorexant.

CYP3A inhibitors

Concomitant administration of BELSOMRA with ketoconazole (a strong CYP3A inhibitor) substantially increased BELSOMRA exposure (2.79-fold change in AUC). Concomitant use of BELSOMRA with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole,

clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin and conivaptan) is not recommended [see Section 4.4 Special Warnings and Precautions for Use, Strong inhibitors of CYP3A; Section 5.2 Pharmacokinetic Properties].

Concomitant administration of suvorexant with diltiazem (a moderate CYP3A inhibitor) also increased suvorexant exposure (2.05-fold change in AUC).

Concomitant administration of BELSOMRA with moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil) is not recommended.

CYP3A inducers

Suvorexant exposure can be substantially decreased when co-administered with strong CYP3A inducers (e.g., rifampin, carbamazepine and phenytoin). The efficacy of BELSOMRA may be reduced [see Section 5.2 Pharmacokinetic Properties].

Effects of suvorexant on other medicines

Suvorexant is a weak inhibitor of CYP3A and the intestinal P-glycoprotein (P-gp) transporter following consecutive, multiple-dose administration.

Midazolam

Concomitant administration of BELSOMRA with midazolam (a sensitive CYP3A substrate) slightly increased midazolam exposure. For most medicines metabolised by CYP3A, BELSOMRA is not expected to increase plasma concentrations to a clinically significant degree [see Section 5.2 Pharmacokinetic Properties].

Digoxin

Concomitant administration of BELSOMRA with digoxin slightly increased digoxin levels due to inhibition of intestinal P-gp. Digoxin concentrations should be monitored as clinically indicated when co-administering BELSOMRA with digoxin [see Section 5.2 Pharmacokinetic Properties].

Other concomitant therapy

No clinically significant pharmacokinetic interactions were observed following co-administration of BELSOMRA with warfarin or oral contraceptives [see Section 5.2 Pharmacokinetic Properties].

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In male and female rats treated orally prior to and during mating and early gestation, decreases were observed in corpora lutea, implantations, and resultant live fetuses. There were no effects in males. At the no-effect dose for females and males, estimated exposures were approximately 25- and 43-times the clinical exposure at the MRHD (20 mg), respectively.

Use in pregnancy (Category B3)

No clinical studies have been conducted in pregnant women. BELSOMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Suvorexant crosses the placenta in rats and rabbits. Teratogenicity was not observed in pregnant rats or rabbits treated orally during the period of organogenesis. In rats, developmental toxicity was limited to a decrease in fetal body weights at maternotoxic doses.

In rabbits, there was no evidence of developmental toxicity. The maternal exposure in rats and rabbits at the no-effect dose was 25-times and 39-times the clinical exposure at the MRHD (20 mg), respectively.

Following oral administration to rats throughout gestation and lactation, effects in the offspring were limited to a transient decrease in body weight; estimated maternal exposure at the no-effect dose was 25-times the clinical exposure at the MRHD (20 mg).

Use in lactation

Available data from a single dose lactation study in 12 women indicate that the transfer of suvorexant and its metabolite, hydroxy-suvorexant, into breast milk is low with a relative infant dose of approximately 0.7% following maternal oral administration. There are no data on the effects of suvorexant on the breastfed infant or the effects on milk production, nor on infant exposure after repeated maternal dosing of suvorexant. Caution should be exercised when suvorexant is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for suvorexant and any potential adverse effects on the breastfed infant from suvorexant or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

See Section 4.4 Special Warnings and Precautions for Use, CNS Depressant Effects, Abnormal thinking and behavioural changes, Abuse and Section 4.8 Adverse Effects (Undesirable Effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies experience in adults

In three Phase 3 clinical studies, 1784 patients were exposed to BELSOMRA, including 160 patients for at least one year. The pooled safety data described below reflects the adverse event profile during the first 3 months of treatment.

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a medicine cannot be directly compared to rates in the clinical trials of another medicine and may not reflect the rates observed in practice.

Adverse events resulting in discontinuation of treatment

The incidence of discontinuation due to adverse events for patients treated with the recommended doses (15 mg or 20 mg) of BELSOMRA, higher doses (30 mg or 40 mg) of BELSOMRA and placebo was 3.0%, 6.2%, and 4.9%, respectively. The most frequent adverse events leading to discontinuation in patients receiving BELSOMRA were somnolence (0.2% BELSOMRA 15 mg or 20 mg; 1.7% BELSOMRA 30 mg or 40 mg; 0.3% placebo) and fatigue (0.2% BELSOMRA 15 mg or 20 mg; 0.7% BELSOMRA 30 mg or 40 mg; 0.0% placebo).

Adverse events observed at an incidence of ≥2% and greater than placebo in controlled trials

Table 1 shows the percentage of patients with adverse events during the first three months of treatment based on the pooled data from the three placebo-controlled clinical studies.

The adverse event profile in elderly patients was generally consistent with non-elderly patients. The adverse events reported during long-term treatment up to 1 year were generally consistent with those observed during the first 3 months of treatment.

Table 1: Percentage of patients with adverse events from three Phase 3 placebo-controlled studies (Incidence ≥2% and greater than placebo during first 3 Months of treatment)

	BELSOMRA (20 mg in non-elderly and 15 mg in elderly)	**BELSOMRA (40 mg in non-elderly and 30 mg in elderly)**	**Placebo**
	N = 493	**n = 1291**	**n = 1025**
General Disorders			
Fatigue	2.2	3.8	1.8
Infections and Infestations			
Upper respiratory tract infection	1.6	2.2	1.2
Gastrointestinal Disorders			
Diarrhoea	2.4	1.6	1.5
Dry mouth	1.8	2.8	1.4
Nausea	1.4	2.1	1.6
Nervous System Disorders			
Dizziness	3.0	2.5	2.8
Somnolence	6.7	10.7	3.0
Headache	7.3	6.6	6.0
Psychiatric Disorders			
Abnormal Dreams	1.8	2.1	1.0
Injury, Poisoning and Procedural Complications			
Medication administration error	3.2	1.9	2.2

In these clinical studies, cough was reported in patients taking BELSOMRA (1.8% BELSOMRA 15 mg or 20 mg; 1.1% BELSOMRA 30 mg or 40 mg; 0.9% placebo). Additionally, in these clinical studies, sleep paralysis and hypnagogic/hypnopompic hallucinations have been reported in patients taking BELSOMRA (<1%).

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of BELSOMRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: palpitations, tachycardia

Gastrointestinal disorders: nausea, vomiting

General disorders and site administration conditions: feeling abnormal

Nervous system disorders: psychomotor hyperactivity

Psychiatric disorders: anxiety, nightmare

Skin and subcutaneous tissue disorders: pruritus

Studies pertinent to safety concerns for hypnotic medicines

Next-day residual effects

Effects of suvorexant on psychomotor performance using Digit-Symbol Substitution Test (DSST): In two Phase 3 confirmatory clinical studies, next day performance was assessed using DSST on the mornings (approximately 9 hours post-dose) following PSG on night 1, month 1, and month 3 of treatment. In the overall population of patients with insomnia treated with BELSOMRA (n=590), no clinically meaningful next day impairment of psychomotor performance was observed compared to placebo.

Driving studies: Two randomized, double-blind, placebo- and active-controlled, four-period crossover studies evaluated the effects of nighttime administration of BELSOMRA on next-morning driving performance 9 hours after dosing in 24 healthy elderly (≥65 years old, mean age 69 years; 14 men, 10 women) and 28 non-elderly (mean age 46 years; 13 men, 15 women) subjects.

The primary outcome measure was change in mean Standard Deviation of Lane Position (SDLP), a measure of driving performance. There was no significant impairment of next-day driving performance as assessed by mean SDLP after one night and 8 consecutive nights of suvorexant dosed at 15 or 30 mg in elderly, 20 or 40 mg in non-elderly subjects. However, some subjects had SDLP changes suggestive of clinically meaningful impaired driving performance following treatment with suvorexant. Across these two studies, five subjects (4 non-elderly women on suvorexant; 1 elderly woman on placebo) prematurely stopped their driving tests due to somnolence. Due to individual variation, patients should be advised not to drive, operate machinery or engage in other activities requiring full mental alertness until fully awake. [See Section 4.4 Special Warnings and Precautions for Use].

Effects on next-day memory and balance in elderly and non-elderly: The effects of suvorexant on next-day memory and balance were evaluated using word learning test and body sway test, respectively, in four placebo-controlled studies following night time administration of suvorexant. Three studies showed no significant effects on memory or balance compared to placebo. In a fourth study in healthy non-elderly subjects, there was a significant decrease in word recall after the words were presented to subjects in the morning following single dose of 40 mg suvorexant; and there was a significant increase on body sway area in the morning following single dose of 20 or 40 mg suvorexant.

Middle of the night safety in elderly subjects

A double-blind, randomised, placebo-controlled study in healthy elderly subjects (n=12) evaluated the effect of a single dose of BELSOMRA on balance, memory and psychomotor performance after being awakened during the night. Night time dosing of BELSOMRA 30 mg did not result in impairment of balance (measured by body sway area) or psychomotor performance (measured by choice reaction time) at 4 and 8 hours post-dose as compared to placebo; a small impairment was seen at 90 minutes post-dose. Memory was not impaired, as assessed by immediate and delayed word recall test at 4 hours post-dose.

Rebound effects

In the combined analysis of three Phase 3 studies in patients with insomnia, rebound insomnia following discontinuation of BELSOMRA relative to placebo and baseline was assessed in non-elderly adult patients receiving BELSOMRA 40 mg or 20 mg and in elderly patients receiving 30 mg or 15 mg. Objective assessments (2 studies) were based on the polysomnographic measures of sleep onset (LPS) and maintenance (WASO) performed the night after treatment discontinuation at Month 3. Subjective assessments (3 studies) were based on patient-reported measures of sleep onset (sTSO) and maintenance (sTST) in the 3 nights following treatment discontinuation at Month 3, Month 6 or Month 12.

Based on the overall assessment of both doses of BELSOMRA evaluated in non-elderly and elderly patients, no effects were seen on measures of sleep onset. Effects were seen on some sleep maintenance measures following BELSOMRA discontinuation but had the characteristics of the return of insomnia symptoms and did not appear to be consistent with clinically meaningful rebound insomnia.

Abuse

In an abuse liability study conducted in recreational polydrug users (N=36), suvorexant (40, 80 and 150 mg) produced similar effects as zolpidem (15, 30 mg) on subjective ratings of "drug liking". As with other hypnotics, care should be taken when prescribing BELSOMRA to individuals with a history of addiction to, or abuse of, drugs or alcohol due to risk of misuse or abuse.

Dependence

In the combined analysis of three Phase 3 clinical studies, when BELSOMRA was discontinued after chronic administration, no clinically meaningful withdrawal was observed. Thus, BELSOMRA does not appear to produce physical dependence.

Withdrawal effects

Potential withdrawal effects following discontinuation of BELSOMRA were assessed in three phase 3 clinical studies in which non-elderly adult patients received BELSOMRA 40 mg or 20 mg and elderly patients received 30 mg or 15 mg. No indication of withdrawal was observed in the overall study population based on assessment of patient responses to the Tyrer Withdrawal Symptom Questionnaire or assessment of withdrawal-related adverse events following the discontinuation of BELSOMRA.

Respiratory safety

Use in Healthy subjects with Normal Respiratory Function: The respiratory depressant effect of suvorexant (40 and 150 mg) was evaluated after one night of treatment in a randomised, placebo-controlled, double-blind, crossover study in healthy non-elderly subjects (n=12). At the doses studied, suvorexant had no respiratory depressant effect as measured by oxygen saturation [see Section 4.4 Special Warnings and Precautions for Use, Patients with compromised respiratory function].

Chronic Obstructive Pulmonary Disease (COPD): The respiratory depressant effect of suvorexant was evaluated after one night and after four consecutive nights of treatment in a randomised, placebo-controlled, 2-period crossover study in patients (n=25) with mild to moderate COPD. Suvorexant (40 mg in non-elderly, 30 mg in elderly) had no respiratory depressant effects in patients with mild to moderate COPD, as measured by oxygen saturation. Clinically meaningful respiratory effects of BELSOMRA in patients with COPD cannot be excluded. BELSOMRA has not been studied in patients with severe COPD [see Section 4.4 Special Warnings and Precautions for Use, Patients with compromised respiratory function].

Obstructive Sleep Apnoea (OSA): The respiratory depressant effect of suvorexant was evaluated after one night and after four consecutive nights of treatment in a randomised, placebo-controlled, 2-period crossover study in patients (n=26) with mild to moderate OSA. Following once-daily doses of 40 mg, the mean Apnoea/Hyponoea Index treatment difference (suvorexant - placebo) on Day 4 was 2.7 (90% CI: 0.22 to 5.09). Clinically meaningful respiratory effects of BELSOMRA in patients with OSA cannot be excluded. BELSOMRA has not been studied in patients with severe obstructive sleep apnoea [see Section 4.4 Special Warnings and Precautions for Use, Patients with compromised respiratory function].

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

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

There is limited premarketing clinical experience with the effects of an overdosage of BELSOMRA. In clinical pharmacology studies, healthy subjects were administered doses of up to 240 mg of suvorexant in the morning with dose dependent increase in frequency and duration of somnolence reported.

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of medication overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed. The value of dialysis in the treatment of overdosage has not been determined. As suvorexant is highly protein bound, haemodialysis is not expected to contribute to elimination of suvorexant.

As with the management of all overdosage, the possibility of ingestion of multiple medications should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Suvorexant is a highly selective reversible high affinity orexin receptor antagonist at OX1R (K_i 0.55 nM) and OX2R (K_i 0.35 nM) receptors.

The orexin neuropeptide signalling system is a central promoter of wakefulness. Orexin-producing neuronal cell bodies localised specifically in the hypothalamus project to the wakefulness mediating neurons of the brain.

Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive. Antagonism of orexin receptors may also underlie potential adverse effects such as signs of narcolepsy/cataplexy. Genetic mutations in the orexin system in animals result in hereditary narcolepsy; loss of orexin neurons has been reported in humans with narcolepsy.

Suvorexant has no direct pharmacological activity or binding affinity (K_i >10 uM) at gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine, or opiate receptors.

Clinical trials

Two randomised, double-blind, placebo-controlled, parallel-group, multicenter questionnaire and polysomnography (PSG) studies assessed the safety, tolerability and efficacy of BELSOMRA in the treatment of adult patients with primary insomnia over a 3 month period. One of these studies had an optional 3-month double-blind extension period in which PSG was not performed. In both studies BELSOMRA was given at doses of 20 mg or 40 mg for patients aged <65 years (mean age 46 years) and at doses of 15 mg or 30 mg for patients aged ≥65 years (mean age 71 years).

In PN028 and PN029, BELSOMRA 15 mg or 20 mg was superior to placebo for sleep latency as assessed both objectively by polysomnography (Table 2) and subjectively by patient-estimated sleep latency (Table 3). BELSOMRA 15 mg or 20 mg was also superior to placebo for sleep maintenance as assessed both objectively by polysomnography (Tables 4 and 5), and subjectively by patient-estimated total sleep time (Table 6). The effects of BELSOMRA at Night 1 (objective) and Week 1 (subjective) were generally consistent with later time points as compared to placebo. Relative to baseline, subjective measures steadily improved through Month 3 (Table 6). Additional analysis of the objective sleep maintenance effect by hour on Night 1 in PN028 and PN029 is shown in Table 7 and demonstrated BELSOMRA treatment decreased the time spent awake after the first hour during Night 1. Improvement compared to placebo was evident for the primary subjective sleep endpoints at timepoints during the 3 month optional extension period.

Table 2: Polysomnographic (PSG) Assessment of Sleep Onset (Latency to Persistent Sleep, LPS) in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† LPS After 1 Night and 1 and 3 Months [minutes]				Difference (and 95% Confidence Interval)† Between Suvorexant and Placebo [minutes]	
Study PN028						
	Placebo (n=290)		Suvorexant 15-20 mg‡ (n=193)			
Baseline	67					
	Post	Change	Post	Change	Change	
Night 1	47	- 20	37	- 30	- 10***	(- 15, - 4)
Month 1	44	- 23	33	- 34	- 10***	(- 16, - 5)
Month 3	40	- 27	32	- 35	- 8**	(- 14, - 2)
Study PN029						
	Placebo (n=286)		Suvorexant 15-20 mg‡ (n=145)			
Baseline	68					
	Post	Change	Post	Change	Change	
Night 1	55	- 13	43	- 25	- 12**	(- 21, - 4)
Month 1	43	- 25	35	- 33	- 8*	(- 15, - 1)
Month 3	39	- 29	39	- 29	0	(- 8, 8)

† Change from baseline, treatment differences, and 95% confidence intervals based upon estimated means; mean baseline is weighted average of baseline means at Night 1; post-baseline mean is sum of baseline and change from baseline means

‡ 15 mg in elderly and 20 mg in non-elderly patients

* p<0.05; **p<0.01; ***p<0.001

Table 3: Patient-estimated Sleep Onset
(Subjective Time to Sleep Onset, sTSO) in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† sTSO After 1 Week and 1 and 3 Months [minutes]				Difference (and 95% Confidence Interval)† Between Suvorexant and Placebo [minutes]
Study PN028					
	Placebo (n=382)		Suvorexant 15-20 mg‡ (n=251)		
Baseline	66				
	Post	Change	Post	Change	Change
Week 1	56	- 10	51	- 15	- 6* (- 10, - 1)
Month 1	54	- 12	49	- 17	- 5 (- 11, 0)
Month 3	49	- 17	43	- 23	- 5* (- 10, 0)
Study PN029					
	Placebo (n=369)		Suvorexant 15-20 mg‡ (n=231)		
Baseline	84				
	Post	Change	Post	Change	Change
Week 1	77	- 7	70	- 14	- 8** (- 13, - 2)
Month 1	70	- 14	63	- 21	- 7* (- 14, 0)
Month 3	63	- 21	56	- 28	- 8* (- 15, 0)

†Change from baseline, treatment differences, and 95% confidence intervals based upon estimated means; mean baseline is weighted average of baseline means at Week 1; post-baseline mean is sum of baseline and change from baseline means

‡15 mg in elderly and 20 mg in non-elderly patients

* p<0.05; **p<0.01; ***p<0.001

Table 4: Polysomnographic (PSG) Assessment of Sleep Time (Total Sleep Time, TST) in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† TST After 1 Night and 1 and 3 Months [minutes]				Difference (and 95% Confidence Interval)† Between Suvorexant and Placebo [minutes]	
Study PN028						
	Placebo (n=290)		Suvorexant 15-20 mg‡ (n=193)			
Baseline	304					
	Post	Change	Post	Change	Change	
Night 1	342	38	384	80	42***	(34, 51)
Month 1	344	40	381	77	37***	(28, 46)
Month 3	354	50	378	74	25***	(15, 34)
Study PN029						
	Placebo (n=286)		Suvorexant 15-20 mg‡ (n=145)			
Baseline	302					
	Post	Change	Post	Change	Change	
Night 1	336	34	383	81	47***	(37, 57)
Month 1	347	45	379	77	32***	(21, 43)
Month 3	354	52	385	83	32***	(20, 43)

† Change from baseline, treatment differences, and 95% confidence intervals based upon estimated means; mean baseline is weighted average of baseline means at Night 1; post-baseline mean is sum of baseline and change from baseline means

‡ 15 mg in elderly and 20 mg in non-elderly patients

* p<0.05; **p<0.01; ***p<0.001

Table 5: Polysomnographic (PSG) Assessment of Sleep Maintenance (Wake After Sleep Onset, WASO) in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† WASO After 1 Night and 1 and 3 Months [minutes]				Difference (and 95% Confidence Interval)† Between Suvorexant and Placebo [minutes]
Study PN028					
	Placebo (n=290)		Suvorexant 15-20 mg‡ (n=193)		
Baseline	117				
	Post	Change	Post	Change	Change
Night 1	97	- 20	65	- 52	- 33*** (- 39, - 26)
Month 1	98	- 19	72	- 45	- 26*** (- 34, - 18)
Month 3	92	- 25	75	- 42	- 17*** (- 25, - 8)
Study PN029					
	Placebo (n=286)		Suvorexant 15-20 mg‡ (n=145)		
Baseline	118				
	Post	Change	Post	Change	Change
Night 1	97	- 21	60	- 58	- 37*** (- 45, - 29)
Month 1	95	- 23	71	- 47	- 24*** (- 33, - 15)
Month 3	93	- 25	62	- 56	- 31*** (- 40, - 22)

† Change from baseline, treatment differences, and 95% confidence intervals based upon estimated means; mean baseline is weighted average of baseline means at Night 1; post-baseline mean is sum of baseline and change from baseline means

‡ 15 mg in elderly and 20 mg in non-elderly patients

* p<0.05; **p<0.01; ***p<0.001

Table 6: Patient-estimated Sleep Time
(Subjective Total Sleep Time, sTST) in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† sTST After 1 Week and 1 and 3 Months [minutes]				Difference (and 95% Confidence Interval)† Between Suvorexant and Placebo [minutes]	
Study PN028						
	Placebo (n=382)		Suvorexant 15-20 mg‡ (n=251)			
Baseline	318					
	Post	Change	Post	Change	Change	
Week 1	333	15	346	28	14***	(7, 20)
Month 1	341	23	357	39	16***	(8, 25)
Month 3	359	41	369	51	11*	(2, 20)
Study PN029						
	Placebo (n=369)		Suvorexant 15-20 mg‡ (n=231)			
Baseline	304					
	Post	Change	Post	Change	Change	
Week 1	318	14	335	31	17***	(9, 25)
Month 1	326	22	347	43	21***	(12, 30)
Month 3	342	38	364	60	22***	(12, 33)

† Change from baseline, treatment differences, and 95% confidence intervals based upon estimated means; mean baseline is weighted average of baseline means at Week 1; post-baseline mean is sum of baseline and change from baseline means

‡ 15 mg in elderly and 20 mg in non-elderly patients

* p<0.05; **p<0.01; ***p<0.001

Table 7: Polysomnographic (PSG) Assessment of Sleep Maintenance (Wake After Sleep Onset, WASO) by Hour on Night 1 in Studies PN028 and PN029

	Mean Baseline, Post-baseline and Change from Baseline† WASO by Hour on Night 1 [minutes]				
Study PN028					
		Placebo (n=290§)		Suvorexant 15-20 mg‡ (n=193§)	
	Baseline	Post	Change	Post	Change
Hour 1	1.5	2.0	0.5	2.1	0.6
Hour 2	8.6	8.0	- 0.6	4.7	- 3.9***
Hour 3	12.5	9.4	- 3.1	5.9	- 6.6***
Hour 4	14.9	11.1	- 3.8	7.1	- 7.8***
Hour 5	15.7	12.5	- 3.2	7.2	- 8.5***
Hour 6	16.4	14.4	- 2.0	9.1	- 7.3***
Hour 7	19.7	15.2	- 4.5	11.4	- 8.3***
Hour 8	30.1	25.6	- 4.5	19.4	-10.7***
Study PN029					
		Placebo (n=286§)		Suvorexant 15-20 mg‡ (n=145§)	
	Baseline	Post	Change	Post	Change
Hour 1	1.8	2.7	0.9	1.5	- 0.3*
Hour 2	9.4	9.3	- 0.1	5.3	- 4.1***
Hour 3	14.0	11.1	- 2.9	6.3	- 7.7***
Hour 4	17.9	12.4	- 5.5	8.2	- 9.7***
Hour 5	16.8	13.0	- 3.8	7.1	- 9.7***
Hour 6	17.8	14.4	- 3.4	8.2	- 9.6***
Hour 7	18.3	14.4	- 3.9	9.0	- 9.3***
Hour 8	24.6	22.4	- 2.2	14.5	-10.1***

† Change from baseline based upon estimated means; mean baseline is weighted average of baseline means at specified hour on Night 1; post-baseline mean is sum of baseline and change from baseline means

‡ 15 mg in elderly and 20 mg in non-elderly patients

§ n is the number of patients included in the analysis of WASO; the number of patients at a particular hour may be lower based upon the number achieving sleep onset by that hour

* p<0.05; **p<0.01; ***p<0.001 compared to placebo change from baseline

BELSOMRA was also evaluated at doses of 30 mg and 40 mg in the 3-month placebo-controlled studies (PN028 and PN029). The higher doses were found to have similar efficacy to lower doses but more adverse reactions were reported at the higher doses.

Evaluation of BELSOMRA on QTc interval

The effects of Suvorexant on QTc interval were evaluated in a randomised, placebo-, and active-controlled (moxifloxacin 400 mg) crossover study in healthy subjects (n=53). The upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 ms based on analysis of suvorexant doses up to 240 mg. Thus, suvorexant does not prolong the QTc interval to any clinically relevant extent.

5.2 PHARMACOKINETIC PROPERTIES

Suvorexant exposure increases in a less than strictly dose-proportional manner over the range of 10-80 mg due to decreased absorption. Suvorexant pharmacokinetics are similar in healthy subjects and patients with insomnia.

Absorption

Suvorexant peak concentrations occur at a median t_{max} of 2.0 hours (range 0.5 to 6.0) under fasted conditions. The mean absolute bioavailability of 20 mg is 62% (5^{th}-95^{th} percentile: 55% to 69%).

Ingestion of suvorexant with a high-fat meal resulted in no meaningful change in AUC or C_{max} and with a delay in t_{max} by approximately 1.5 hours. Suvorexant may be taken with or without food.

Distribution

The mean volume of distribution of suvorexant is approximately 49 litres. Suvorexant is extensively bound (>99%) to human plasma proteins and does not preferentially distribute into red blood cells. Suvorexant binds to both human serum albumin and α1-acid glycoprotein.

Metabolism

Suvorexant is mainly eliminated by metabolism, primarily by CYP3A with a minor contribution from CYP2C19. The major circulating entities are suvorexant and a hydroxy-suvorexant metabolite. This metabolite is not expected to be pharmacologically active.

Excretion

The primary route of elimination is through the faeces, with approximately 66% of radiolabeled dose recovered in the faeces compared to 23% in the urine. Suvorexant is eliminated primarily in the form of metabolites, with <1% of the dose recovered in faeces and urine as suvorexant.

The systemic pharmacokinetics of suvorexant are linear with accumulation predictable from single-dose data. Steady-state is achieved by 3 days following once-daily dosing and is consistent with a mean $t_{1/2}$ of approximately 12 hours (95% CI: 12.0 to 13.1).

Special populations

Gender, age, body mass index (BMI), and race were included as factors assessed in the population pharmacokinetic model to evaluate suvorexant pharmacokinetics in healthy subjects and to predict exposures in the patient population. Age and race are not predicted to have any clinically meaningful changes on suvorexant pharmacokinetics.

Suvorexant exposure is higher in females than in males. In females, the AUC and C_{max} are increased by 17% and 9%, respectively, following administration of BELSOMRA 40 mg. The average concentration of suvorexant 9 hours after dosing is 5% higher for females across the dose range studied (10-40 mg).

Apparent oral clearance of suvorexant is inversely related to body mass index. In obese patients, the AUC and C_{max} are increased by 31% and 17%, respectively. The average concentration of suvorexant approximately 9 hours after a 20 mg dose is 15% higher in obese patients (BMI > 30 kg/m^2) relative to those with a normal BMI (BMI ≤ 25 kg/m^2).

In obese females, the AUC and C_{max} are increased by 46% and 25%, respectively, compared to non-obese females.

The effects of renal and hepatic impairment on the pharmacokinetics of suvorexant were evaluated in specific pharmacokinetic studies.

Suvorexant exposure after a single dose was similar in patients with moderate hepatic impairment (Child-Pugh category 7 to 9) and healthy matched control subjects; however, the suvorexant apparent terminal half-life was increased from approximately 15 hours (range 10 - 22 hours) in healthy subjects to approximately 19 hours (range 11 - 49 hours) in patients with moderate hepatic impairment. BELSOMRA was not studied in patients with severe hepatic impairment and is not recommended in these patients [see Section 4.2 Dose and Method of Administration, Patients with hepatic impairment].

Suvorexant exposure (expressed as total and unbound concentrations) was similar between patients with severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73 m^2: CKD stage 4 or 5) and healthy matched control subjects [see Section 4.2 Dose and Method of Administration, Patients with renal impairment].

Medicine related interactions

CNS-active medicines
An additive effect on psychomotor performance was observed when a single dose of 40 mg of suvorexant was co-administered with a single dose of 0.70 g/kg alcohol. Suvorexant did not affect alcohol concentrations and alcohol did not affect suvorexant concentrations [see Section 4.4 Special Warnings and Precautions for Use, Abnormal thinking and behavioural changes, CNS depressant effects and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, CNS-active agents].

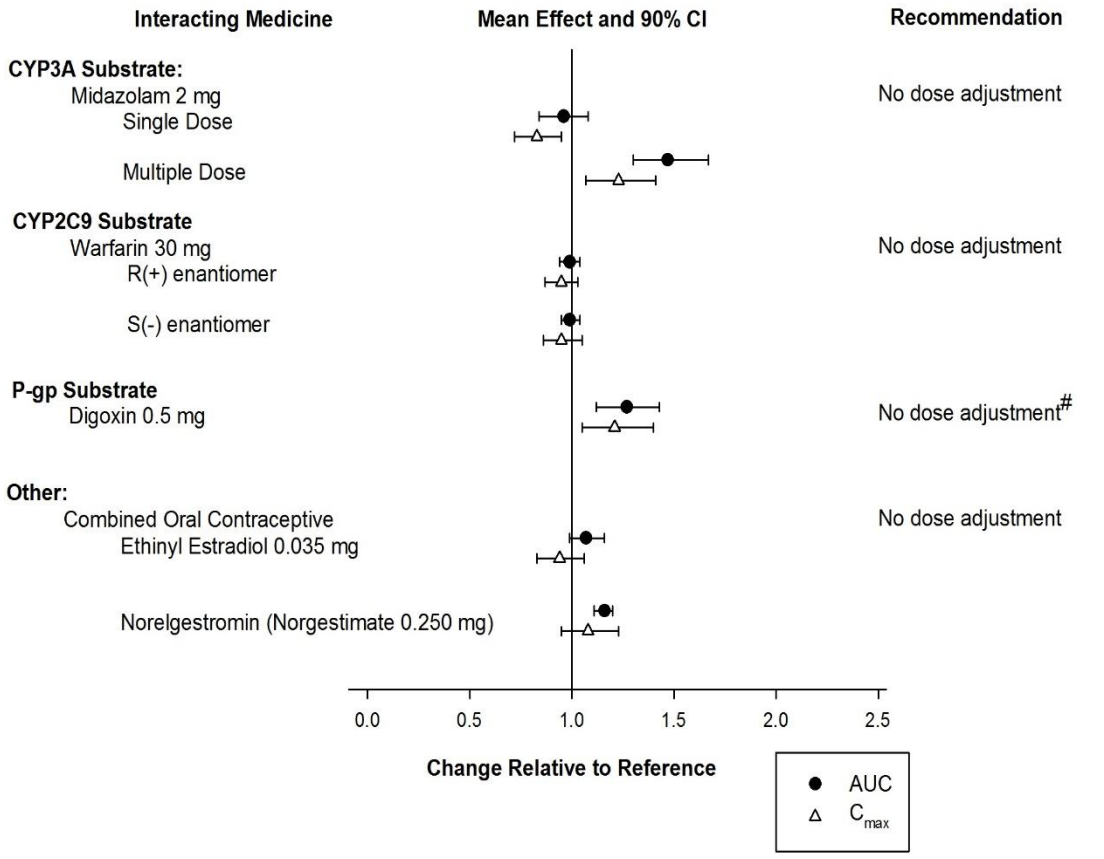
An interaction study with single dose of 40 mg suvorexant and paroxetine 20 mg at steady-state levels in healthy subjects did not demonstrate a clinically significant pharmacokinetic or pharmacodynamic interaction [see Section 4.4 Special Warnings and Precautions for Use, Abnormal thinking and behavioural changes, CNS depressant effects and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, CNS-active agents].

Effects of other medicines on suvorexant
Strong CYP3A inhibitors (e.g., ketoconazole) significantly increased suvorexant exposure (2.79-fold change in AUC). Moderate CYP3A inhibitors (e.g., diltiazem) also increased suvorexant exposure (2.05-fold change in AUC). Strong CYP3A inducers (e.g., rifampin) substantially decreased suvorexant exposure [see Section 4.4 Special Warnings and Precautions for Use, Strong inhibitors of CYP3A and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects of other medicines on suvorexant].

Effects of suvorexant on other medicines
In vitro metabolism studies indicate that suvorexant has a potential to inhibit CYP3A and intestinal P-gp. Suvorexant is unlikely to cause clinically significant inhibition of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. In addition, no clinically meaningful inhibition of OATP1B1, BCRP and OCT2 transporters is anticipated. Chronic administration of suvorexant is unlikely to induce the metabolism of medicines metabolised by major CYP isoforms. Specific *in vivo* effects on the pharmacokinetics of midazolam, warfarin, digoxin and oral contraceptives are presented in Figure 1 as a change relative to the interacting medicine administered alone (test/reference) [see Section 4.5 Interactions with

Other Medicines and Other Forms of Interactions, Effects of suvorexant on other medicines, Other concomitant therapy].

Figure 1: Effects of suvorexant* on the pharmacokinetics of co-administered medicines



* Suvorexant 40 mg was evaluated in all studies, except midazolam where 80 mg suvorexant was administered

\# Monitor digoxin concentrations as clinically indicated [see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions, Effects of suvorexant on other medicines]

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Suvorexant was negative in *in vitro* (bacterial reverse mutation, alkaline elution, and chromosomal aberration in Chinese Hamster Ovary cells) and *in vivo* (rat and mouse micronucleus) genotoxicity assays.

Carcinogenicity

No evidence of carcinogenic potential was observed in hemizygous Tg.rasH2 mice dosed orally for 6 months; a separate kinetic study suggested that exposures achieved were up to 105-times the clinical exposure at the MRHD (20 mg).

In the 2-year carcinogenicity study in rats, there was an increased incidence of hepatic and thyroid follicular cell adenomas. These changes were secondary to hepatic enzyme induction and increased TSH production, respectively, which are mechanisms well-described to be rodent-specific. At the no-effect dose for tumours, exposure was 7-times the clinical exposure (plasma AUC) at the MRHD (20 mg).

In the rat carcinogenicity study, there was an increased incidence of very slight to slight retinal atrophy at exposures (plasma AUC) 11 times or greater the clinical exposure at the MRHD (20 mg); at the no-effect dose, exposure was 7-times clinical exposure. This retinal change was of the same type and severity found in untreated aged rats. The mechanism involved in this change and its clinical significance are not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet contains the following inactive ingredients: copovidone, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate.

In addition, the film coating contains the following inactive ingredients: lactose monohydrate, hypromellose, titanium dioxide and triacetin.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

BELSOMRA is available in aluminium/aluminium blister packs of 10*, and 30 film-coated tablets. BELSOMRA is also available in starter packs of 3* tablets.

* Not currently supplied in Australia

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

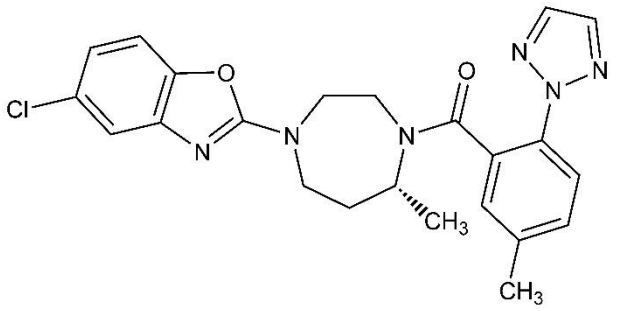
Suvorexant is a white to off-white powder that is insoluble in water. pKa is 2.19±0.02. The log of the distribution (partition) coefficient at pH 7 of suvorexant is log D (pH 7) = 3.73±0.01.

Suvorexant is described chemically as:

[(7*R)*-4-(5-chloro-2-benzoxazolyl)hexahydro-7-methyl-1*H*-1,4-diazepin-1-yl][5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone.

Its empirical formula is $C_{23}H_{23}ClN_6O_2$ and the molecular weight is 450.92.

Chemical structure



CAS number

The CAS Registry Number is 1030377-33-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

16 November 2016

10 DATE OF REVISION

22 July 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Section on lactation updated to include data supporting that suvorexant enters mother's breast milk.
	Updated year in Copyright statement

RCN: 000026995-AU