



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Suvorexant

Proprietary Product Name: Belsomra

Sponsor: Merck Sharp and Dohme Australia Pty
Ltd

March 2015

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of commonly used abbreviations

Abbreviation	Meaning
AASM	American Academy of Sleep Medicine
AE	Adverse experience
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APAT	All Patients as Treated
APTS	All patients treated set
AUC	Area under the concentration-time curve
AUC _{0-inf}	Area under the concentration-time curve from time 0 to infinity
AUC _{0-last}	Area under the concentration-time curve from time 0 to last observation
BBB	Blood-brain barrier
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
BZD	Benzodiazepine
CI	Confidence interval
CL	Clearance
C _{max}	Maximum concentration
CRT	Choice Reaction Time
CSSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DBP	Diastolic Blood Pressure
DSCT	Digit Symbol Copy Test
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorder-Category IV-Text Revision

Abbreviation	Meaning
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
FAS	Full analysis set
FDR	False discovery rate
FMI	Final market image
FSG	Fasting serum glucose
GCP	Good clinical practice
GI	Gastrointestinal
GMR	Geometric mean ratio
hCG	Human chorionic gonadotropin
HR	Heart rate
HRT	Hormone replacement therapy
IA	Interim analysis
IEC	Independent Ethics Committee
IM	Intramuscular
IN	Intranasal
IP	Intraperitoneal
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IUD	Intrauterine device
IV	Intravenous
IVRS	Interactive Voice Response System
KSS	Karolinska Sleepiness Scale
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LPLV	Last patient last visit

Abbreviation	Meaning
LPS	Latency to persistent sleep
LREM	Latency to REM
LS means	Least-squares means
LSWS	Latency to slow wave sleep
MAR	Missing at random
MED	Minimal effective dose
MRM	Multiple reaction monitoring
MSE	Mean square error
msec	millisecond
MVAV	Motor Vehicle Accidents and Violations
NAW	Number of awakenings
NOA	Number of arousals
NREM	Non-REM
NSAID	Nonsteroidal anti-inflammatory drug
NSS_W_1	Number of stage shifts to wake or stage 1
NSSL	Number of shifts to lighter stages of sleep
OTC	Over the counter
PBO	Placebo
PSG	Polysomnography
PD	Pharmacodynamic
PDLOC	Predefined limits of change
PK	Pharmacokinetic
QIDS	Quick Inventory of Depressive Symptomatology
QTcB	Corrected QT interval, Bazet's
QTcP	Population specific rate method of correcting QT interval
RBC	Red blood (cell) count

Abbreviation	Meaning
REM	Rapid eye movement
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard deviation
SDLP	Standard Deviation of Lateral Position
SDS	Sheehan Disability Scale
SE	Sleep efficiency
SEM	Standard error of the mean
siDMC	Standing internal data monitoring committee
sNAW	Subjective number of awakenings
SOL	Sleep Onset Latency
SRT	Simple Reaction Time
sTSO	Subjective time to sleep onset
sTST	Subjective total sleep time
SVT	Suvorexant
SWA	Slow wave activity
sWASO	Subjective wake after sleep onset
SWS	Slow wave sleep
t ^{1/2}	Half-life
TIB	Time in bed
T _{max}	Time to maximum effect or concentration
TSO	Time to sleep onset
TST	Total Sleep Time
TTA	Total time awake
ULN	Upper limit of normal
VAS	Visual analog scale

Abbreviation	Meaning
Vss	Volume of distribution at steady state
WASO	Wake after sleep onset
WBC	White blood (cell) count

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Rejected
<i>Date of initial TGA decision:</i>	17 April 2014
<i>Date of final TGA decision:</i>	5 September 2014 ¹
<i>Active ingredient:</i>	Suvorexant
<i>Product name:</i>	Belsomra
<i>Sponsor's name and address:</i>	Merck Sharp and Dohme Australia Pty Ltd Level 1 Building A 26 Talavera Rd Macquarie Park NSW 2113
<i>Dose form:</i>	Immediate release film coated tablets
<i>Strengths:</i>	15 mg, 20 mg, 30 mg and 40 mg
<i>Container:</i>	Foil blisters
<i>Pack sizes:</i>	10 or 30 tablets/blister pack. A starter pack of 3 tablets proposed.
<i>Approved therapeutic use:</i>	Not applicable
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	Not applicable
<i>ARTG number:</i>	Not applicable

Product background

This AusPAR describes the application by the sponsor Merck Sharpe and Dohme Pty Ltd (Australia) (MSD) to register the new chemical entity suvorexant, an orexin receptor antagonist, under the trade name Belsomra for the following indication:

Treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

The sponsor proposes suvorexant be administered immediately before bedtime with or without food at the following dosages:

¹ Subject to the *Administrative Appeals Tribunal Act 1975*, the sponsor has at this stage made an application to the Administrative Appeals Tribunal (AAT) for a review of this decision. This AusPAR will be updated with the outcome of the AAT when known.

Non-elderly adults: 40 mg suvorexant once daily. A lower dose of 20 mg once daily may be appropriate for some patients based on individual tolerability. The dose should not exceed 40 mg per day.

Elderly: 30 mg suvorexant once daily. A lower dose of 10 mg once daily may be appropriate for some patients based on individual tolerability. The dose should not exceed 30 mg per day.

Suvorexant tablets may be taken with or without food and should be taken immediately before bedtime.

Suvorexant is the first in a class of selective antagonist for orexin receptors (OX1R and OX2R). Orexin neurons were discovered in 1998 and found to have widespread projections to basal forebrain, monoaminergic and cholinergic brainstem and spinal cord regions. The orexin system has been implicated in the regulation of behaviours associated with wakefulness, locomotion and feeding.

Suvorexant is purported to act by blocking the binding of the wake-promoting neurotransmitters orexin A and orexin B to OX1R and OX2R. This inhibits activation of wakefulness promoting neurons of the arousal system, and thereby facilitating the physiological process by which the brain transitions from wake to sleep. Suvorexant has no pharmacological affinity for receptors that bind to gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine or opiates.

Currently registered hypnotic agents include various benzodiazepines, zopiclone, zolpidem and melatonin are all for short term use. Diphenhydramine, an antihistamine is also available over-the-counter as a temporary sleep aid. With the exception of melatonin, dependency is of concern for all the above actives. Melatonin, has a very restricted indication and limited demonstrated efficacy.

The trade name Belvasom was proposed as an alternative to the originally proposed name Vispli, following advice from the clinical evaluator that the latter was unacceptable due to its similarity to Vistil.

Regulatory status

This is an application for a new chemical entity.

The international regulatory status of suvorexant at the time of this AusPAR is tabulated in Table 1 below.

Table 1. International regulatory status

Country	Registration status	Comments	Approved Dosage and Administration
United States of America	US FDA Complete response letter received 1 st July 2013	A Complete Response Letter summarizes the FDA review and their concerns, and lists requirements for the resubmission for subsequent NDA review and approval.	US FDA: Use the lowest dose effective for the patient. Recommended dose is 10 mg, no more than once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20
United States of America	Approved	Re-submission included quality data supporting the 5mg and 10mg tablet strengths using the same original clinical efficacy and safety data package as agreed to by FDA. Two additional PK studies were	

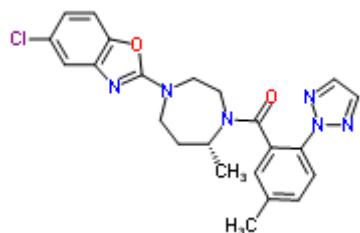
Country	Registration status	Comments	Approved Dosage and Administration
		included in the review. This was a Class 2 resubmission.	mg once daily. CYP3A4 inhibitors: Recommended dose is 5 mg when used with moderate CYP3A inhibitors. Dose can be increased to 10 mg once daily if the 5 mg dose is not effective. Not recommended for use in patients taking strong CYP3A inhibitors.
Canada	Withdrawn. 4 February 2013	Health Canada requires additional clinical data to support the 15/20 mg doses.	Not applicable
Japan	Approved	PMDA requested availability of a 10 mg dose post approval.	The usual dose for the adult and the elderly is respectively 20 mg and 15 mg orally administered once a day just before going to bed.

II. Quality findings

Drug substance (active ingredient)

Suvorexant (designated MK-4305 by the company; structure reproduced below) has one chiral centre, and is manufactured by chemical synthesis.

Figure 1. Chemical structure of suvorexant



Two enantiotropically related anhydrous polymorphs have been identified; Forms I and II. Although Form I is more stable at 25°C, Form II has been chosen for commercial development as it is easier to process.

The drug substance is claimed to be Biopharmaceutics Classification System (BCS) Class II.² A bidirectional transport experiment using Caco-2 monolayers indicates that suvorexant has an apparent permeability which is greater than the high permeability reference compound metoprolol.

Three impurities [including the minor (*S*)-enantiomer] are controlled in the drug substance; each is limited to the International Conference on Harmonisation of Technical

² Class II - high permeability, low solubility. The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.

Requirements for Registration of Pharmaceuticals for Human Use qualification limit³ in the active pharmaceutical ingredient (API) specification.

Drug product

The drug products are immediate release film coated tablets containing suvorexant (SVT) at four different strengths; 15 mg, 20 mg, 30 mg or 40 mg.

All tablet strengths will be marketed in blisters packs of 10 and 30 tablets in each. A starter pack of 3 tablets is also proposed (all strengths).

The tablet cores are direct scales. No overage is employed.

As early clinical data indicated that the peak plasma concentration (C_{max}) was lower and the time to C_{max} (T_{max}) delayed with no change in area under the plasma concentration versus time curve (AUC) when a suvorexant 10 mg formulation was administered with food, development efforts subsequently focussed on mitigation of this potential pH-dependent/food effect. Upon further development, the 'Preliminary Marketing Formulation (PMF)/Final Market Image (FMI)' pH-independent polymer formulation(s) were used in Phase IIb and Phase III studies (and in the majority of Phase I studies).

The stability data support a shelf life of 24 months stored below 25°C to the tablets packaged in the polyvinyl chloride (PVC)/aluminium/oriented polyamide (OPA)/aluminium blisters proposed for Australia.

The common release and expiry limit proposed for unspecified degradants ($\leq 0.2\%$) in the finished products is consistent with the ICH guideline qualification limit⁴, based on a maximum recommended daily dose of 40 mg and has been accepted on that basis.

An in-process test for moisture at batch release (limit: $\leq 40\%$ relative humidity (RH)) is performed using Frequency Modulated Infrared Spectroscopy (FMS) following film-coating.

Biopharmaceutics

The PMF was designed to mitigate the potential pH-dependent solubility/food effect observed in pilot food effect assessments with the Phase I Fit-for-Purpose (FFP) formulation. The FMI formulation (the intended commercial formulation) is compositionally identical to the PMF, with no change in functional excipients and only a minor decrease in the level of magnesium stearate lubricant from 0.5% to 0.25% and the addition of a colorant to the non-functional film coat. It was used in the pivotal Phase III trials as well as selected late stage Phase I studies. Given the similarities between the PMF and FMI formulations and the utilisation of both formulations in the pivotal efficacy and safety studies, a bioequivalence study was not considered necessary to support development.

Six biopharmaceutics studies relating to bioavailability, bioequivalence and food effect were provided, as summarised below.

Study 007 (Biocomparison Pharmacokinetic Study)

Study 007 was an open-label, randomised, partially-fixed sequence, 5-period cross-over study to (1) evaluate the comparative pharmacokinetics of three preliminary marketing formulations (PMFs) of SVT (P1, P2 and P3) with those from the FFP formulation used in the initial Phase I studies (T1) to support selection of a biocomparable formulation for use

³ CPMP/ICH/2737/99 Note for Guidance on Impurities in New Drug Substances (Revision).

⁴ CPMP/ICH/2738/99 "Note for Guidance on Impurities in New Drug Products (Revision)"

in future clinical studies, and (2) to compare the pharmacokinetic profile of the tablet formulations of SVT under fed and fasting conditions.

Key pharmacokinetic parameters for plasma SVT are summarised below.

Table 2. Pharmacokinetic parameters for plasma SVT

Protocol	Study Objectives	Study Design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (95% Confidence Interval)							Geometric Mean Ratio (95% CI)		
					C _{max} (μM)	T _{max} (hr) ^a	Apparent Terminal t _{1/2} (hr) ^b	AUC _{0-<i>inf</i>} (μM·hr)	AUC _{0-24h} (μM·hr)	AUC _{0-<i>tau</i>} (μM·hr)	CL (mL/min)	V _{dss} (L)	C _{max}	AUC _{0-<i>inf</i>}
007	Assess and compare the pharmacokinetics of 4 formulations	A 5-Period, Crossover, Single Dose Study, 4 Formulations	T1, 40-mg	17	1.672 (1.439, 1.943)	2.0 (0.5 - 4.0)	10.5 (4.6)	16.76 (13.26, 21.19)	11.98 (10.36, 13.87)	4.34 (3.78, 4.99)	--	--	P1, P2 or P3 / T1	
			P1, 40-mg	18	1.531 (1.321, 1.775)	2.0 (1.0 - 4.0)	10.3 (4.1)	17.26 (13.66, 21.80)	12.42 (10.74, 14.37)	4.07 (3.55, 4.67)	--	--	0.92 (0.82, 1.03)	1.03 (0.95, 1.12)
			P2, 40-mg	18	1.199 (1.035, 1.390)	2.0 (1.0 - 4.0)	12.0 (4.5)	17.30 (13.70, 21.85)	11.62 (10.05, 13.44)	3.57 (3.11, 4.09)	--	--	0.72 (0.64, 0.81)	1.03 (0.95, 1.12)
			P3, 40-mg	17	1.278 (1.100, 1.485)	1.0 (1.0 - 4.0)	10.2 (3.7)	17.70 (14.00, 22.38)	12.22 (10.56, 14.14)	3.84 (3.34, 4.41)	--	--	0.7 (0.68, 0.86)	1.06 (0.97, 1.15)
			P1, 40-mg Fed	6	1.208 (0.885, 1.648)	4.0 (0.5 - 6.0)	11.6 (6.1)	19.30 (11.97, 31.10)	--	--	--	--	0.82 (0.57, 1.18)	1.18 (1.01, 1.37)
			P2, 40-mg Fed	6	1.401 (1.014, 1.936)	2.0 (2.0 - 4.0)	10.0 (4.1)	15.70 (10.80, 22.84)	--	--	--	--	1.23 (1.13, 1.34)	1.06 (0.86, 1.32)
			P3, 40-mg Fed	5	1.356 (1.013, 1.815)	4.0 (2.0 - 4.0)	9.5 (2.0)	16.38 (13.58, 19.74)	--	--	--	--	1.00 (0.87, 1.14)	1.02 (0.90, 1.16)

The C_{max} and AUC 90% confidence interval (CI) for formulation P1 (a scale up of the FFP formulation) were contained within the pre-specified interval of 0.70 to 1.43.

The AUC 90% CI for formulations P2 and P3 (containing SVT as the hydrochloric acid (HCl) salt) were within the pre-specified interval of 0.70 to 1.43. A modest decrease in C_{max} of approximately 24 to 28% was observed. T_{max} values were considered broadly similar across all formulations.

As variability in the range of geometric mean ratios was reduced for formulation P2 relative to those estimated for P1 and P3, this formulation was selected for further development.

Study 018 (IV and Oral Dose Proportionality Study)

This was an open-label, randomised, two-part study in healthy male and female subjects (n = 48) to determine proportionality of SVT pharmacokinetics following IV and oral administration. Subject participation was limited to one study part.

In Part I, four panels of subjects (n = 8 per panel) were administered single-rising doses of 5 mg (Panel 1), 10 mg (Panel 2), 20 mg (Panel 3) and 30 mg (Panel 4) of SVT via IV infusion over 1 h (Panels 1 to 3) or 1.5 h (Panel 4). The lowest dose of 5 mg in Panel 1 was selected *a priori*, the succeeding doses of 10, 20, and 30 mg were based upon ongoing review and modelling of the pharmacokinetics from each of the treatment panels to provide exposures approximating those anticipated following respective oral doses of 15 mg, 40 mg and 80 mg.

Part II of the study, in which 16 healthy subjects received 10, 20, 40, and 80 mg SVT tablets (the commercial formulation) according to a randomised, open-label, 4-period cross-over design (≥ 7 days washout between each treatment period) provided the definitive dose proportionality assessment over an oral dose range of 10 mg to 80 mg. Key pharmacokinetic parameters are summarised below.

Table 3. Pharmacokinetic parameters for SVT

Protocol	Study Objectives	Study Design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (95% Confidence Interval)							Geometric Mean Ratio (95% CI)		
					C _{max} (μM)	T _{max} (hr) ^a	Apparent Terminal t _{1/2} (hr) ^a	AUC _{0-<i>inf</i>} (μM·hr)	AUC _{0-30hr} (μM·hr)	AUC _{0-4hr} (μM·hr)	CL (mL/min)	V _{dss} (L)	C _{max}	AUC _{0-<i>inf</i>}
018	Assess plasma PK and dose proportionality of four, single, intravenous and oral doses	Open-label, randomized, two-part study in healthy male and female subjects	5-mg IV	8	0.543 (0.470, 0.627) ^b	--	9.2 (3.4)	3.46 (2.78, 4.32)	--	--	52.28 (42.00, 65.08)	36.51 (31.20, 42.72)	--	--
			10-mg IV	8	1.044 (0.904, 1.206) ^b	--	9.9 (5.2)	6.92 (5.54, 8.63)	--	--	52.72 (42.35, 46.69)	42.46 (36.39, 47.72)	--	--
			20-mg IV	8	1.751 (1.516, 2.023) ^b	--	13.5 (5.0)	15.10 (12.11, 18.84)	--	--	48.60 (39.04, 60.50)	57.12 (48.81, 66.84)	--	--
			30-mg IV	8	1.900 (1.645, 2.194) ^b	--	8.9 (1.7)	13.73 (11.00, 17.13)	--	--	80.82 (64.76, 100.36)	57.33 (48.99, 67.08)	--	--
			10-mg Oral (P2)	16	0.456 (0.403, 0.516)	1.5 (1.0 - 4.0)	12.1 (1.8)	5.32 (4.55, 6.23)	--	--	--	--	--	--
			20-mg Oral (P2)	16	0.648 (0.572, 0.721)	1.0 (1.0 - 4.0)	12.5 (2.6)	9.51 (8.12, 11.14)	--	--	--	--	--	--
			40-mg Oral (P2)	16	0.956 (0.845, 1.082)	2.0 (1.0 - 4.0)	12.6 (2.5)	16.21 (13.85, 18.98)	--	--	--	--	--	--
			80-mg Oral (P2)	16	1.518 (1.342, 1.717)	2.0 (0.5 - 6.0)	13.6 (2.9)	27.26 (23.28, 31.91)	--	--	--	--	--	--

Summary statistics for intravenous (IV) SVT parameters are tabulated below.

Table 4. Pharmacokinetic parameters for IV SVT

Assessment of Dose Proportionality of Suvorexant (MK-4305) Following Administration of Single IV-Infusion of 5 to 30 mg in Healthy Male and Female Subjects (N=8 per dose)

Parameter	Dose Range	Slope Estimate (90% CI)	Expected Fold-Change (90% CI) ^a	Expected Fold-Change with Perfect Dose-Proportionality
AUC _{0-<i>inf</i>}	5-30 mg	0.84 (0.69, 0.99)	4.48 (3.43, 5.84)	6
	5-20 mg	1.06 (0.87, 1.26)	4.36 (3.32, 5.72)	4
	10-30 mg	0.68 (0.44, 0.92)	2.11 (1.62, 2.74)	3
C _{max} ^b	5-20 mg	0.84 (0.72, 0.97)	3.23 (2.70, 3.85)	4

^a Fold change for highest dose/lowest dose based on results from the power model and assessment of dose proportionality over this dose range.
^b Due to the different infusion time for 30 mg relative to the other doses, 30-mg data was not included in the assessment for dose proportionality for C_{max}.
^b C_{max} (concentration at the end of the infusion).
Equivalence boundaries for the AUC_{0-*inf*} slope from 5-30 mg are (0.61, 1.39).

The slope and 90% CI from the power model AUC from time 0 to infinity (AUC_{0-*inf*}) fell within the pre-specified equivalence boundaries of 0.61 and 1.39, a range based on the ratio of the highest and lowest IV doses studied and equivalence boundaries of (0.50, 2.00) for the dose-adjusted AUC_{0-*inf*} ratio.

A less than dose proportional increase in exposure over the dose range is evident, driven largely by the exposures observed at the 30 mg IV dose which were lower than expected based on the 5 mg to 20 mg IV dose exposures. The company claimed that this may be influenced by inter-panel differences due to the limitations of conducting the study as a parallel design. The observed results from the supplemental assessment of dose proportionality suggest that exposures over the 5 mg to 20 mg dose range more closely approximate dose-proportionality as compared to the 5 mg to 30 mg dose range. In addition, exposures in the 5 mg to 20 mg IV dose range approximated those of the 15 mg to 40 mg oral dose range investigated in the Phase III studies.

Summary statistics for oral SVT parameters are tabulated below.

Table 5. Pharmacokinetic parameters for oral SVT

Assessment of Dose Proportionality of Suvorexant (MK-4305) Following Single Oral Dose Administration of 10 to 80 mg in Healthy Male and Female Subjects (N=16)

Parameter	Dose Range(mg)	Slope Estimate (90% CI)	Expected Fold-Change (90% CI) [†]	Expected Fold-Change with Perfect Dose-Proportionality
AUC _{0-∞}	10-80	0.78 (0.70, 0.86)	5.10 (4.32, 6.03)	8
	10-40	0.80 (0.68, 0.93)	3.05 (2.57, 3.61)	4
	20-80	0.76 (0.63, 0.89)	2.87 (2.38, 3.45)	4
C _{max}	10-80	0.58 (0.51, 0.64)	3.32 (2.90, 3.80)	8
	10-40	0.53 (0.43, 0.64)	2.10 (1.82, 2.42)	4
	20-80	0.62 (0.51, 0.73)	2.35 (2.01, 2.73)	4

[†] Fold change for highest dose/lowest dose based on results from the power model and assessment of dose proportionality over this dose range.

Equivalence boundaries for the AUC_{0-∞} slope from 10-80 mg are (0.67, 1.33).

The slope and 90% CI from the power model AUC_∞ fell within the pre-specified equivalence boundaries of 0.67 and 1.33, a range based on the ratio of the highest and lowest oral doses studied and equivalence boundaries of (0.50, 2.00) for the dose-adjusted AUC_{0-∞} ratio. Similar to the trend observed with IV doses, there is evidence that increases in exposure are not strictly dose proportional over this dose range, as the confidence interval for the slope lies below 1.0.

The less than dose proportional increase in SVT exposure observed for the 10 mg to 40 mg dose range and 10 mg to 80 mg dose range may be due to absorption limitations.

Study 020 (bioavailability and food effect study)

Study 020 was an open-label, randomised 2-period cross-over study in healthy male and female subjects (n = 14) designed to evaluate the effect of food on SVT pharmacokinetics.

Key pharmacokinetic parameters for plasma SVT are summarised below.

Table 6. Pharmacokinetic parameters for plasma SVT

Protocol	Study Objectives	Study Design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (95% Confidence Interval)							Geometric Mean Ratio (95% CI)		
					C _{max} (μM)	T _{max} (hr) [‡]	Apparent Terminal t _{1/2} (hr) [‡]	AUC _{0-4hr} (μM·hr)	AUC _{0-8hr} (μM·hr)	AUC _{0-24hr} (μM·hr)	CL (mL/min)	V _{dss} (L)	C _{max}	AUC _{0-∞}
020	Evaluate the effect of food on suvorexant plasma pharmacokinetics	Open-label, randomised, 2-period crossover study in healthy male and female subjects	40-mg Fasted (P2)	13	0.983 (0.790, 1.224)	2.0 (1.0 - 4.0)	10.9 (3.4)	13.19 (10.60, 16.41)	--	--	--	--	Fed/fasted	
			40-mg Fed (P2)	13	1.074 (0.862, 1.337)	3.0 (1.0 - 6.0)	11.6 (3.6)	12.99 (10.44, 16.16)	--	--	--	--	1.09 (0.90, 1.33)	0.98 (0.91, 1.07)

AUC_{0-∞} and C_{max} were largely unchanged after administration with a high-fat breakfast compared to fasted conditions. A small, statistically significant increase in median T_{max} was observed following SVT administration with food; however, apparent terminal half-life (t_{1/2}) was largely similar under both conditions.

Study 041 (biocomparison study)

Study 041 was a randomised, open-label, 4-period cross-over study to evaluate the comparative pharmacokinetics of four batches of SVT tablets (commercial formulation) and the impact of tablet hardness. The test and reference batches used in this study were quantitatively identical, differing only in compression force used during their manufacture.

A secondary objective was to compare in vitro disintegration time and dissolution to the in vivo pharmacokinetics to establish an In-vitro in-vivo correlation (IV-IVC).

In each period, healthy male or female subjects (n = 12), received one of each of the four formulation batches A, C (Reference Phase III material), D and E as a single oral dose of 40 mg SVT following an overnight fast. Statistical data are reproduced below.

Table 7. Statistical analysis of suvorexant pharmacokinetic parameters following a single dose of 40 mg of 4 different formulations

Statistical Analysis of Suvorexant (MK-4305) Pharmacokinetics Following Single Dose Administration of 40 mg Suvorexant (MK-4305) as Three Test Formulations (A, D, E) and Reference Phase III Formulation (C) to Healthy Subjects (N=12)

Pharmacokinetic Parameter	Geometric Mean [†] for Treatment (% CV)				Geometric Mean (90% CI for GMR) for Treatment Ratio			rMSE [‡]
	Formulation A	Formulation C	Formulation D	Formulation E	A/C	D/C	E/C	
AUC _{0-∞} (μM·hr)	21.56 (24.3)	22.11 (23.5)	21.32 (23.6)	22.64 (18.5)	0.98 (0.89, 1.07)	0.96 (0.88, 1.06)	1.02 (0.93, 1.12)	0.134
C _{max} (μM)	1.59 (35.1)	1.48 (23.2)	1.29 (40.0)	1.28 (14.7)	1.07 (0.90, 1.28)	0.87 (0.73, 1.04)	0.86 (0.72, 1.03)	0.252
AUC _{0-t_{max}} (μM·hr)	4.09 (30.5)	3.95 (22.5)	3.45 (36.2)	3.43 (22.8)	1.04 (0.90, 1.19)	0.87 (0.76, 1.01)	0.87 (0.75, 1.00)	0.194
T _{max} (hr) [§]	1.3 [0.5, 5.0]	1.8 [1.0, 3.0]	1.5 [1.0, 5.0]	1.3 [1.0, 5.0]	--	--	--	
Apparent t _{1/2} (hr)	14.9 (4.8)	15.1 (3.6)	15.0 (5.1)	15.9 (5.0)	--	--	--	

[†] Back-transformed least squares means from mixed effects model performed on natural log-transformed values (% CV).
[‡] rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. rMSE*100% approximates the within-subject % CV on the raw scale.
[§] Median [Min, Max].
^{||} Harmonic Mean (Jack-Knife Standard Deviation).

AUC_{0-∞} was generally similar for each of the test formulations relative to the reference ('Formulation C'). The observed mean C_{max} for the test formulations with higher hardness (D, E) were approximately 13 to 14% less than that for the mean of the reference (C), whereas the observed mean C_{max} for the test formulation with lower hardness (A) was approximately 7% greater than that for the mean of the reference (C).

The changes in C_{max} between the test (A, D and E) and reference (C) formulations appear to principally contribute to the observed differences in partial AUC, suggesting that the impact of tablet hardness on absorption is adequately captured by C_{max}.

Study 042 (japanese food study)

This was an open-label, 2-period, nonrandomised cross-over study in healthy Japanese male and female subjects (n=12) to evaluate the effect of a Japanese breakfast, which has lower caloric and fat content relative to a high fat meal, on SVT pharmacokinetics.

Statistical analysis indicated that AUC_{0-∞} and C_{max} were largely unchanged after administration with a standard Japanese breakfast relative to the fasted state.

Study 051 (tablet interchangeability across dose strengths)

Study 051 was a two-part, single-dose, randomised, two-treatment, cross-over, two-stage adaptive design study in healthy male or female subjects (n = 120) to evaluate the relative bioavailability of different dose strengths of SVT FMI tablets (the intended commercial formulation). Subjects only participated in one part of the study (n = 60 per part). Part I compared 2 x 15 mg tablets (Treatment A) with 1 x 30 mg tablet (Treatment B); Part II compared 2 x 20 mg tablets (Treatment C) with 1 x 40 mg tablet (Treatment D). Although comparative dissolution profiles were not provided from the biobatches, the evaluator concluded from the similarity of the profiles across the physiological pH range (and using the regulatory method), and from the biopharmaceutic outcomes of the study that this need not be pursued.

To compare Treatment A to Treatment B and Treatment C to Treatment D, two-sided 94.12% confidence intervals for the true differences in means for log-transformed AUC from time 0 to time T (AUC_{0-t}), AUC_{0-∞} and C_{max} (for example, Treatment A - Treatment B and Treatment C -Treatment D) were calculated using the mean square error from the

linear mixed-effects model and referencing a t-distribution. These confidence limits were exponentiated to obtain the 94.12% confidence intervals for the $AUC_{0-\infty}$ and C_{max} of the true geometric mean ratios. This is consistent with the guidance regarding two-stage design adopted by the TGA.

The company's results for C_{max} and $AUC_{0-\infty}$ from both Parts were independently verified by the evaluator, who concurred with MSD's conclusions that the pharmacokinetics of suvorexant following single-dose administration of two SVT 15 mg tablets and one SVT 30 mg tablet (Part I), and following single-dose administration of two SVT 20 mg tablets and one SVT 40 mg tablet (Part II) are each considered bioequivalent, as assessed by $AUC_{0-\infty}$ and C_{max} .

Quality summary and conclusions

There are no objections in respect of Chemistry, Manufacturing, Controls and Biopharmaceutics to registration of these products.

III. Nonclinical findings

Introduction

The quality of the nonclinical dossier was broadly satisfactory. The pharmacological studies demonstrated receptor selectivity, dose-dependent sleep effects and safety in central nervous system (CNS), cardiovascular and respiratory systems. The findings of some pharmacology studies (as indicated in main body) were however presented as summaries with minimal data, as such it was not possible to confirm the veracity of the original data. In some toxicological studies, data from which the conclusions were drawn were also not available (indicated in main body).

All relevant pivotal studies were Good laboratory practice (GLP) compliant and consistent with relevant ICH guidelines.

Pharmacology

Primary pharmacology

Suvorexant imparts its actions by reversibly binding to orexin Receptors 1 and 2 (OX1R and OX2R) and inhibiting the binding of receptor specific ligands (orexins). Suvorexant binding blocks orexin stimulated intracellular calcium release, thus, potentially decreasing wake time and increasing both rapid eye movement (REM) and non-REM sleep.

In vitro studies comparing orexin receptor binding revealed lower binding affinity of suvorexant at human receptors compared to most test species (except dog at OX1R (affinity (K_i) 0.41 nM versus human 0.55 nM) and rabbit at OX2R (K_i 0.32 nM versus human 0.35 nM). The metabolites M9, M16 and M17 showed lower receptor binding affinities for each receptor compared to suvorexant (6.3 fold (M9) to 645 fold (M17)). Of these 3 metabolites, M9 showed the greatest affinity (approximately 6 to 7 fold less than parent drug). The antagonist potencies (increased intracellular calcium levels) of the M9 and M16 metabolites were comparable to that of suvorexant, while M17 was approximately 4 times less potent at human and rat OX1R and OX2R receptors. Despite the antagonist activities of the metabolites, however, the lower binding affinities and also poor penetration into the CNS (see *Pharmacokinetics* below) would greatly limit the potential for the metabolites to contribute to the pharmacological activity of suvorexant *in vivo*.

The efficacy of suvorexant in vivo was assessed in rat, dog and monkey models. In rats, dose-dependent reductions in active wake and concomitant increase in Delta and REM sleep was noted at 30 and 60 mg/kg intraperitoneal (IP) doses. In dogs, reductions in active wake times (30%) and increase in slow wave sleep (96%), delta sleep (150%) and REM (47%) sleep were noted when 3 mg/kg doses of suvorexant was administered. Monkey studies also revealed an increase in Delta sleep I and REM sleep from 0.5 to 30 mg/kg/day. Limited data from dogs did not show pharmacological activity of M9, at similar doses to suvorexant.

No accompanying cataplexy in dogs was noted in these studies and no effect on food intake or weight was noted in Diet Induced Obese (DIO) mice up to 100 mg/kg (PO, four times a day (QID)).

Based on primary pharmacology studies, the administered doses of suvorexant appeared to favour sleep behaviour with no clinical signs. However, the orexin receptors are not exclusive to neurons involved maintenance of wakefulness, and have been implicated in energy homeostasis and vigilance and dopaminergic reward system (ventral tegmental nucleus). As such, the evaluator believes the subtle effects of suvorexant on other neural circuits (impacting emotion, reward, and energy homeostasis⁵) were not investigated or discussed in depth.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic studies revealed minimal cross reactivity of suvorexant and its metabolites M9 and M17 with common enzymes and receptors, indicating high selectivity for the orexin receptors. Notable targets of interest were: dopamine transporter (DAT), adenosine A3 receptors and the (hERG) potassium channel. The strongest inhibition was noted in DAT (73%) at 10 µM concentrations. DAT also returned 50% inhibitory concentration (IC₅₀) and K_i values of 10 µM and K_i of 7.96 µM against M9 metabolite, while no responses were noted for the M17 metabolite. The steady state plasma C_{max} values of suvorexant and the M9 metabolite are 1.1 and 0.9 µM, respectively. Since both entities are highly protein bound in plasma (approximately 99.5%), the sponsor proposes reduced risk of DAT inhibition by clinical doses of suvorexant, which is acceptable.

Specialised safety pharmacological studies covering the CNS, cardiovascular and respiratory systems were conducted in accordance with the ICH guidelines. In rat studies, CNS signs noted included flattened posture or sternal recumbency, ataxia, decreased muscle tone/line crossing/rearing/mean body temperature and slow aerial/surface righting. The no No Observable Effect Level (NOEL) was determined in doses ranging from 80 to 1200 mg/kg. In cardiovascular studies, suvorexant was found to reversibly inhibit hERG current with an IC₅₀ at 2.6 µM and 20% inhibitory concentration (IC₂₀) at 0.66 µM. Although these values are close to the plasma C_{max} (1.1 µM), suvorexant is ≥99% bound to plasma proteins and these IC₅₀ and IC₂₀ values are approximately 470 times and 120 times, respectively, the free plasma concentration in humans.

While statistically significant increases in QT and QTc intervals⁶ were noted in dogs, the changes were deemed unrelated to treatment given their sporadic distribution and being

⁵ Natsuko Tsujino & Takeshi Sakurai, *Pharmacological Reviews*, June 2009 vol. 61 no. 2, 162-176

⁶ In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia.

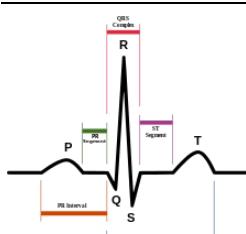
within limits of natural variation, which is acceptable. The IV dog study reported a suvorexant C_{max} of 23.8 μM (22 times clinical C_{max}). Systemic exposure was not measured in the PO dog study but based on the Day 1 plasma C_{max} values in male dogs receiving 400 mg/kg PO in Study TT076037 (suvorexant 16.7 μM , M9 8.4 μM), likely exposures achieved in the PO study would have approximated 15 times and 10 times the respective clinical C_{max} values of 1.1 μM and 0.856 μM . No test article-related respiratory effects were noted. No renal or gastro intestinal safety studies were provided.

Pharmacokinetics

The oral bioavailability for rats and dogs was approximately 48% and approximately 34% respectively. In rats, complete absorption was deduced based on similarity of radioactive dose recovered in bile and urine following IV and PO administration. The approximately 48% bioavailability was attributed to first pass extraction. In dogs however, the lower bioavailability is likely due to slow absorption, as indicated by a smaller fraction of radioactivity recovered in bile and urine following PO administration as compared to IV. In humans, estimated bioavailability (%) is comparable to rats and dogs at doses ≥ 40 mg (compared to 37% to 47%). At doses < 40 mg, bioavailability was higher than the test species (compared to 63% to 82%). The estimates are consistent with the less than dose proportional AUC and C_{max} values often noted in the rat and dog repeat toxicity studies, particularly at high doses. Terminal elimination $t_{1/2}$ of suvorexant was 0.8 and 3.8 h in rats and dogs, respectively. T_{max} was relatively rapid (compared to 0.4 to 2.5 h in most instances) in both species with rapid clearance generally observed at low doses. The mean plasma clearance (CL_p) following IV administration was 35.3 and 3.5 mL/min/kg for the two respective species.

Plasma protein binding was generally high in all species with unbound suvorexant not exceeding 5% in all species. The general protein binding trend for all species was as follows; human < dog = monkey = rat < mouse < rabbit. In humans, plasma protein binding was $\geq 99\%$ across a range of concentrations, including clinically relevant concentrations. Similar protein binding characteristics were also noted for M9 and M17 metabolites (only rat and human were compared for M17). No changes in protein binding were noted in hepatic or renal insufficiency patients.

Distribution of radioactively labelled (^{14}C)-suvorexant was broad and rapid. In Sprague-Dawley (SD) rats dosed with 20 mg/kg (PO) of ^{14}C -suvorexant, radioactivity was detected in tissues ranging from contents of small intestine, cecum, large intestine, stomach, and oesophagus, bile, urine, liver, renal medulla, adrenal gland, kidney, renal cortex, olfactory lobe and brain cerebrum at 1 h postdose. The data indicate an ability for suvorexant to cross the blood-brain-barrier with an average tissue/plasma ratio for the CNS of 10% (based on 0.5 to 1.0 h post dose data). No suvorexant was selectively associated with pigmented tissue in rat studies. In rat and rabbit studies suvorexant readily crossed the placenta (rats and rabbits) and was excreted into milk in rats. Suvorexant (0.5 μM) was not a P-gp substrate in rat or human (B-A/A-B ratio⁷; 1.2 and 1.0, respectively) with high



⁷ P-gP substrates and non-substrates are classified on the basis of the B-A/A-B apparent permeability; a P-gP substrate will be effluxed from the basolateral (B) to the apical (A) side of the membrane and will therefore have a greater permeability from B-A than A-B, resulting in a flux ratio >1 .

passive permeability in LLC-PK1 cells. Both metabolites M9 and M17, however, were p-glycoprotein (P-gp) substrates in human, rat and mouse with transport ratios (B-A/A-B) ranging from 2.7 to 11.4, and the results in P-gp competent and deficient mice indicate very low CNS penetration by M9.

The key metabolic pathways of suvorexant included oxidation, hydroxylation (M8, M9, 10a), bis-hydroxylations (M6a, b and c, M7b and c), dechlorination (M16 and M17). In addition dog hepatocytes included a glucuronide of M10a (M12), a glucuronide of M9 (M11), and an apparent water addition (M20). All metabolites found in human were represented in mouse, rat, rabbit or dog, either in microsome or hepatocyte studies. All human metabolites were present in dog, and all but M17 were present in rat. M9 was present in all species examined. The metabolism of suvorexant in human liver microsomes was found to be predominantly mediated by cytochrome P450 isoform 3A4 (CYP3A4) and at higher concentrations CYP2C19. Metabolism was the primary mode of elimination in rats and dogs.

Excretion studies in rats and dogs revealed 94% and 85% of the total dose to be excreted, mostly as bile, and then urine and faeces. In lactating rats, excretion of suvorexant was detected in the milk at concentrations up to 9.3-fold greater than maternal plasma concentrations (80 mg/kg/day, maximum dose 200 mg/kg/day). The M9 metabolite was also detected in milk at concentrations slightly higher than maternal plasma.

Overall, the pharmacokinetic profile of the test species used in the pivotal studies is adequately suited for the study.

Pharmacokinetic drug interactions

Suvorexant is a time-dependent inhibitor of CYP3A4 (k_{inact} and K_i values of 0.14 min⁻¹ and 12 μ M, respectively) and its metabolite, M9 was also a time-dependent inhibitor of CYP3A4 (k_{inact} and K_i values of 0.052 and 0.078 min⁻¹ at 10 μ M and 50 μ M, respectively). Inhibition of 3A4 (suvorexant IC₅₀ 4.0 μ M, M9 IC₅₀ 11 μ M) and 2C19 (IC₅₀ 5.3 μ M, suvorexant only) was considered modest. A dose-related induction in CYP3A12 and CYP3A26 was also observed; at 10 μ M suvorexant, CYP3A12 and CYP3A26 induction was 16.8 and 16.4 fold greater than the vehicle control, respectively. In human hepatocytes, suvorexant induced increases in CYP3A4, 1A2 and 2B6 mRNA. Neither suvorexant nor M9 were potent inhibitors of human Breast Cancer Resistance Protein (BCRP), Organic anion transporting polypeptide 1B1 (OATP1B1) or organic cation transporter 2 (OCT2), except for suvorexant with (IC₅₀ 1.3 μ M).

With the free (unbound) plasma C_{max} of suvorexant at \leq 11 nM, these data suggest a low potential for drug interactions under clinical conditions.

Toxicology

Acute toxicity

While no specific single dose studies were performed, single dose toxicity was assessed during repeat dose toxicity studies in rat, rabbit and dog, including range-finding studies.

Repeat-dose toxicity

Multiple mouse, rat and dog repeat dose toxicity studies were submitted for suvorexant. Studies ranged from 7 days to 9 months in duration and included two 26 week rat and 9 month dog study each. The rat and dog pivotal studies met ICH guidelines and were GLP compliant. All 26 week and 9 month studies used the clinical route of delivery and dosing frequency. Given the limited mortality rates, the number of animals was adequate for the

study durations. While the maximum tolerated dose (MTD) was greater than the high dose in dog studies, owing to a test article related death at high dose in rats, the MTD is likely to be 80 mg/kg/day.

Relative exposure

Exposure ratios (ER) have been calculated based on animal: human plasma AUC_{0-24h} for total drug (Table 8). The exposure ratios (comparable between the pivotal and non-pivotal studies) were adequate.

Table 8. Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Sex	Dose mg/kg/day	AUC _{0-24 h} µM·h	Exposure ratio [^]
Rat (SD)	1 month (TT079815)	M	100	24.0	1.67
			300	75.2	5.25
			1200	136	9.51
		FM	100	85.1	0.70
			300	298	1.67
			1200	619	2.88
	1 month (TT081160)	M	80	62.5	4.4
			160	192	13.4
			325	434	30.3
			1200	381	26.6
		FM	80	198	13.8*
			160	406	28.4
	6 months (TT081052)		325	760	53.1
		M	100	69.2	4.8*
			300	201	14.1
			1200	405	28.3
		FM	25	45.5	3.2
			75	227	15.9
			300	646	45.2
	6 months\$	M	80	87.6 [23.3]	6.1 [2.4]

Species	Study duration	Sex	Dose mg/kg/day	AUC0-24 h $\mu\text{M}\cdot\text{h}$	Exposure ratio [^]
	(TT091033)		160	178 [30.8]	12.4 [3.2]
			325	396 [43.9]	27.7 [4.6]
		FM	30	72.3 [6.5]	5.1 [0.7]
			80	212 [14.3]	14.8 [1.5]
			325	695 [35.6]	48.6 [3.7]
	2 years (TT096025) (Carc.)	M	80	62.3	4.4*
			160	105	7.3
			325	335	23.4
		FM	40	101	7.1*
			80	163	11.4
			325	539	37.7
Dog (Beagle)	1 month (TT0081159)	M	60	354	24.8
			60	491	34.3
			125	798	55.8
			250	897	62.7
		FM	800	557	39.0
			60	354	24.8
			125	701	49.0
			250	1150	80.4
	1 month (TT076037)	M	10	32.5	2.3
			30	65.6	4.6
			400	402	28.1
		FM	10	48.1	3.4
			30	106	7.4
			400	319	22.3
	9 month	M	5	48.1	3.4

Species	Study duration	Sex	Dose mg/kg/day	AUC0-24 h $\mu\text{M}\cdot\text{h}$	Exposure ratio [^]
	(TT081051)		25	186	13.0
			800	607	42.4
		FM	5	28.8	2.0
			25	161	11.3
			800	799	55.9
	9 month\$ (TT091062)	M	10	105 [60.5]	7.3 [6.3]
			50	388 [253]	27.1 [26]
			125	847 [495]	59.2 [52]
		FM	10	79.1 [665]	5.5 [7.0]
			50	440 [290]	30.8 [30]
			125	708 [410]	49.5 [43]
Human (healthy volunteers)	Steady state		40 mg	Suvorexant: 14.3# M9: 9.55&	–

* = NOAEL was below lowest dose
 ^ = animal:human plasma AUC0-24 h (metabolite M9 values are in [])
 # = Module 2.7.2, Summary of Clinical Pharmacology Studies, Tables 38-40
 & = Reference P003, day 14 data
 \$ = pivotal study

It is also noted that exposure ratios for free (unbound) drug would be somewhat greater, since plasma protein binding in human plasma at clinical concentrations ($\geq 99.5\%$) was slightly greater than that in the test species (96 to 99%).

Major toxicities

The identified target organs were the liver (rat, dog) and the thyroid (rat), in both sexes. Increased hepatocellular hypertrophy was noted in both sexes in 6 month rat studies at mid and high doses (ERs approximately 14; at the No observable adverse effect levels (NOAELs) for this effect, ER 3 to 6). The hypertrophy was often accompanied by increased liver size. Hepatocellular hypertrophy was also noted in two 4 week studies of which in one study, hypertrophy was noted in both sexes at doses greater than 160 mg/kg/day (ER 13 to 28; at the NOAELs for this effect, ER 4 to 14). In contrast, increased liver size and hypertrophy was only observed in females in the other 4 week study (ER approximately 2), with no clear signs of hypertrophy in male treatment groups, probably because of lower systemic exposure in this study (ER up to approximately 9). A general pattern of the repeat dose studies was a graded increase of these liver effects with escalating dosage.

An increased incidence of thyroid follicular cell hypertrophy was also noted in both sexes in the 4 week and 6 month rat studies, concomitant with the hepatocellular hypertrophy

(so the ERs in the paragraph above are applicable for this change also). The thyroid response was considered secondary to hepatic enzyme induction and corroborated by the thyroxine clearance study in rats.

The pattern of effects seen in rats was less pronounced in dogs. In the pivotal 4 week and 9 month dog studies, there were mostly low incidences of increased liver weight and hepatocellular hypertrophy at the higher doses (ERs > approximately 30). The ERs at the NOAELs for the liver effects were 6 to 13 in the 9 month studies. Though these occurrences were within the historical range, given the demonstrated capacity of the test article to induce a hypertrophic liver response in rodents, a relationship to treatment is not excluded. Liver changes were more marginal in the 4 week pivotal dog study (possibly resulting from the shorter exposure). The relatively mild liver changes (and absent thyroid histopathology) in dogs contrasted with the rat results, supporting the hypothesis that hypothalamo-pituitary-thyroid axis effects are pronounced in rats (confirmed in the rat carcinogenicity study). In one 4 week dog study, atrophy of the prostate was noted in doses ≥ 30 mg/kg/day, but in the absence of confirmatory findings in other studies, this is considered not to be test-article related.

Systemic exposure to the M9 metabolite was measured in some of the repeat dose toxicity and reproductive toxicity studies (Tables 8 and 9). Animal: human exposure ratios achieved were much lower for M9 than suvorexant in rats but similar in dogs and rabbits. However, as M9 is unlikely to contribute significantly to the activity of suvorexant *in vivo* (lower receptor affinities; poor CNS penetration (discussed above)); these M9 ratios have not been incorporated in the draft Product Information statements.

The other major observation from the repeat dose studies was treatment-related clinical signs, reasonably attributed to exaggerated pharmacological responses.

Genotoxicity

Submitted genotoxicity studies included in vitro bacterial reverse mutation assays and in vivo and in vitro chromosomal aberration assays. The bacterial reverse mutation assay utilised the appropriate strains of bacteria, concentration ranges and validation controls, and it was established that the M9 metabolite was produced by the S9⁸ metabolic activation system under the in vitro test conditions. No genotoxicity was noted in the bacterial reverse mutation assay. In in vitro chromosomal aberration assays significant cytotoxicity (≥ 105 μ M) was noted. While most assessment parameters for chromosomal aberration were negative or within historical control, a slight increase in endoduplication was noted above the historical level.

No genotoxicity was noted in the in vivo chromosomal aberration studies in mice and rats. At high doses (500 and 1000 mg/kg) test article related clinical signs were noted, consistent with previous studies.

Overall, no suvorexant (or M9 metabolite) related genotoxicity was detected, under these test conditions.

Carcinogenicity

Two carcinogenicity studies were conducted, in transgenic mice (27 weeks) and SD rats (104 weeks). The respective maximum feasible doses were 650 and 325 mg/kg/day PO.

⁸ The S9 fraction is the product of an organ tissue (usually liver) homogenate used in biological assays. The S9 fraction has been used in conjunction with the Ames test to assess the mutagenic potential of chemical compounds. Chemical substances sometimes require metabolic activation in order to become mutagenic. Furthermore the metabolic enzymes of bacteria used in the Ames test differ substantially from those in mammals. Therefore to mimic the metabolism of test substance that would occur in mammals, the S9 fraction is often added to the Ames test.

The route of administration and frequency were congruent with the intended clinical application. The studies were GLP compliant and utilised appropriate numbers of animals for studies of their respective durations. In the rat carcinogenicity study, while survival rates to termination were less than the recommended ICH guidelines⁹, no difference was observed between control and treatment groups, no test article-association was observed, and the deaths occurred during the latter half of the study.

In the 27 week transgenic mouse study, while no test-article related neoplastic lesions were observed, disproportionately high incidences of lung and spleen nodules were noted in gross examination in the 25 mg/kg/day group in both sexes. No remarkable histopathological observations were associated with these nodules. The positive control (urethane) elicited the expected neoplastic responses. Exposure determinations were limited to plasma concentrations; however, a separate kinetic study (096038) suggested that AUC exposures achieved were up to 67 times the clinical exposure. M9 exposure was measured only at 7 days (Study 096038), but animal/human margins were also quite high (≥ 50 times) at the 650 mg/kg/day dose.

In the 2 year rat study, a statistically significant increase in hepatocellular adenomas was noted in males at 325 mg/kg/day; a low incidence also at 160 mg/kg/day was probably a threshold effect. (A low incidence of hepatocellular carcinoma in 325 mg/kg/day rats was within historical control ranges). A similar increase in thyroid follicular cell adenomas was noted in both sexes at the same 325 mg/kg dose, and also in males at 160 mg/kg/day. In the liver, all dose groups were associated with hepatocellular hypertrophy and focal eosinophilic cellular alteration, while in the thyroid, follicular cell hypertrophy and focal hyperplasia were observed in almost all dose groups. These changes are attributed to suvorexant-induced hepatic enzyme induction resulting in increased hepatic thyroxine clearance leading to disruption of the hypothalamo-pituitary-thyroid axis and increased thyroid stimulating hormone (TSH) levels. Supporting evidence for this mechanism was obtained in the thyroxine clearance study in rats (TT#11-1020). The resultant liver and thyroid gland changes in the rat carcinogenicity study, derived from increased hepatic thyroxine metabolism and increased TSH levels, is a well-known rat-specific response, considered of limited relevance to human risk assessment¹⁰. While the susceptibility of rats to this mechanism may limit their suitability as the second animal in long term carcinogenicity studies, no other tumorigenic responses were detected in this study. At the NOEL dose for adenomas (80 mg/kg/day), the animal/human exposure ratio (plasma AUC) was 4.

Very slight-slight retinal atrophy was observed in the rat carcinogenicity study, at ≥ 160 mg/kg/day in males and ≥ 80 mg/kg/day in females; the increased incidence at 40 mg/kg/day in females, although within the historical control range, was also likely to be attributable to treatment, given the clear response at higher doses. The plasma AUC exposure at the lowest dose for this effect was approximately 7 times clinical exposure (approximately 4 times clinical exposure at the NOEL). This retinal effect, typical of a spontaneous change in aged albino rats, thus appeared to be somewhat exacerbated by suvorexant treatment. The clinical significance of this finding in rats is not known, and no related safety signal has been reported in the late stage clinical database (Safety Specification, Risk Management Plan). Nevertheless, inclusion of this information in the Product Information document is warranted, as proposed by the sponsor.

Reproductive toxicity

Reproductive toxicity studies included two fertility and early embryonic studies in rat (15 days prior to co-habitation through to Gestational day (GD) 7 [♀] and 6 weeks [♂]), two

⁹ 3BS7a: Note for Guidance on Carcinogenic Potential

¹⁰ McClain (1989) Toxicologic Pathology, 17, 294-306

embryofetal development studies each in rat (GD6-GD20) and rabbit (GD6-GD20) and one pre/postnatal development study in rat (GD6-, GD15, GD20 and lactation day (LD) 20). In addition one rat and rabbit study on placental transfer and excretion into milk was also performed. All studies were GLP compliant and consistent with relevant ICH guidelines.

In the TPGS fertility and early embryonic development study, no suvorexant-related effects on fertility or reproductive performance were noted in males up to 1200 mg/kg/day, while in females a decrease in mean corpora lutea, mean uterine implantations and live fetuses per litter were observed at 1200 mg/kg/day, so the NOEL was 75 mg/kg/day. Systemic exposure was not measured in these studies; however, based on the exposure data from rat study TT081052 (Table 8 above), exposure at the NOEL dose for these effects in females would have approximated 16x clinical exposure, with *ca* 28x clinical exposure at the male NOEL dose. In the SDF fertility study, effects were limited to a likely threshold effect on corpora lutea, implantations and live fetuses at the 325 mg/kg/day dose. Based on exposure data from rat Study TT091033 (Table 8), exposure ratios at the NOEL doses (males 325 mg/kg/day, females 80 mg/kg/day) would have approximated 28 times in males and 15 times in females, giving consistent safety margins across the two studies.

Table 9. Relative exposure in reproductive toxicity studies

Study	Species & Study strain; sampling regimen; no./time point	Dose mg/kg/day; PO	AUC _{0-24h} µM·h	Exposure ratio [^]		
TT087190	Rat (SD); 6 over 0.5-24h; n=3 ♀	Embryofetal development	30	30.9		
			150	279		
			1000	853		
TT107100	Rat (SD); 6 over 0.5-24h; n=6 ♀	Embryofetal development Suvorexant	30	76.8		
			80	230		
			325	794		
	Rabbit (DB); 6 over 0.5-24h; n=3 ♀	Embryofetal development M9	30	6.16		
			80	11.3		
			325	24.0		
TT087200			30	0.6		
			80	1.2		
			325	2.5		
TT107090	Rabbit (DB); 6 over	Embryofetal development Suvorexant	40	29.9		
			100	95.7		
			300	255		
			50	46.6		
			150	361		
				17.8		
				3.3		
				25.2		

Study	Species & Study strain; sampling regimen; no./time point		Dose mg/kg/day; PO	AUC _{0-24h} μM·h	Exposure ratio [^]
	0.5-24h; n=6 ♀		325	647	45.2
		Embryofetal development M9	50	57.6	6.0
			150	234	24
			325	314	33
TT117220	Rat (SD); 6 over 0.5-24h; n=6 ♀	Pre/postnatal development Suvorexant	200	447	31.3
		Pre/postnatal development M9	200	20.6	2.2
Human (healthy volunteers)	Steady state		40 mg	Suvorexant: 14.3 [#] M9: 9.55 ^{&}	

[^] = animal: human plasma AUC_{0-24h} for suvorexant and M9

[#] = Module 2.7.2, Summary of Clinical Pharmacology Studies, Tables 38-40

[&] = Reference P003, Day 14 data

Bolded doses are embryofetal NOAELs

Embryofetal development studies were conducted in rats and rabbits, with adequate dosing and exposure but no evidence of teratogenicity reported in either test species. In the rat studies, the NOAEL for maternal toxicity was consistently 30 mg/kg/day across studies, while the only notable fetal observation was reduction in weight at doses exceeding the maternal NOAELs; 1000 mg/kg/day and 325 mg/kg/day. At the respective fetal NOELs of 150 and 80 mg/kg/day, ERs were 19 times and 16 times. The M9 ERs (SDF study) were lower than for suvorexant (1.2 at 80 mg/kg/day, 2.5 at 325 mg/kg/day) (Table 9).

In the TPGS rabbit embryofetal development study, maternal toxicity was found at 300 mg/kg/day (NOEL 100 mg/kg/day), along with some evidence of fetal toxicity (incomplete ossification) at 100 and 300 mg/kg/day. In the SDF rabbit study, the NOAEL for maternal toxicity was 50 mg/kg/day and the NOAEL for embryofetal development was 150 mg/kg/day (ER 25 times for suvorexant, similar for M9). The very low incidences of malformations (palate dysplasia, thoracoschisis, omphalocele and vestigial tail) noted at 100 and 300 mg/kg/day (1 and 2 incidences, respectively) were considered incidental, and there was no clear confirmation of the ossification findings of the other rabbit study. In the rat and rabbit embryofetal development studies, suvorexant-related fetal toxicity was generally observed only at doses exceeding the maternal NOAEL.

In the rat postnatal development study, transient weight loss in pups was noted at 200 mg/kg/day (ER 31 times) at pre-weaning. No other pre/postnatal development effects

were noted, so the NOAEL was 80 mg/kg/day (estimated ER >10 times, based on ER at 200 mg/kg/day).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3¹¹, which is acceptable.

Local tolerance and other toxicity studies

Dermal irritation

Suvorexant was negative in a rabbit dermal irritation study and lymph node screening assays.

Corneal opacity and permeability

In a bovine corneal opacity and permeability test using a 20% suvorexant solution, suvorexant was classified as a mild irritant (in vitro score of 3.46).

Dependence

The abuse potential of suvorexant was assessed in female rats administered up to 325 mg/kg/day PO (ER approximately 38; female kinetic data, study TT096025). While changes in some measured behavioural parameters were suggestive of a possible diminutive withdrawal syndrome, the overall evidence for a 'discontinuation syndrome' was considered to be negative in this animal model. Exposure was not measured, but based on data from studies TT091033 and TT096025, AUC exposures of suvorexant and M9 were estimated at approximately 40 times and 4 times clinical exposure at the 325 mg/kg dose.

In a drug discrimination study involving zolpidem and morphine trained female rats, suvorexant demonstrated a dose related partial generalisation to the zolpidem cue at mid (80 mg/kg) and high (325 mg/kg) doses. No generalisation to the morphine cues was noted at any dose. The sponsor considered the appearance of partial generalisation to zolpidem as likely '*...the result of changes in direct drug-induced changes in motor function or sedation properties of all three drugs in these rats*'. The significance of this possible interpretation is not clear, but the lack of generalisation to the morphine cue suggests low dependence potential.

In a self-administration monkey study using methohexitone, no consistent pattern of IV self-administration of suvorexant (tested up to 0.5 mg/kg/infusion) was noted.

Taken together, the available nonclinical data present minimal/no convincing evidence for dependence potential with suvorexant. Confirmation from clinical data, however, should be obtained.

Cataplexy

In dog studies utilising suvorexant and other orexin receptor antagonists, signs consistent of cataplexy (hindlimb buckling, forelimb buckling and sternal recumbency with adequate response to stimuli and decreased activity) were reported following food enrichment. A dose-escalating 28 day PO study with suvorexant in dogs confirmed these observations, at doses of 5 mg/kg/day (one instance only) and 30 mg/kg/day (several animals), following food enrichment. Respective (AUC, C_{max}) exposures were 2 times and 6 times clinical exposure at the 5 mg/kg/day dose, and 11 times and 17 times clinical exposure at 30

¹¹ Category B3: Drugs which have 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 fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

mg/kg/day. A further, short term monkey study, however, revealed no cataplexy-related signs up to 70 mg/kg/day PO for 3 days, achieving respective AUC exposures to suvorexant and M9 of 7x and 17x clinical values (C_{max} exposures of 13 times and 2 times clinical exposure). However, given the short-term nature of the monkey study, it is difficult to definitively conclude if the cataplectic signs observed are limited to canine studies. The clinical significance of these observations is not known. It is noted that the draft Product Information document indicates that suvorexant has not been studied in patients with cataplexy, and is not recommended in such patients.

Phototoxicity

No suvorexant-related phototoxicity (assessed as ocular and skin histopathology) was noted in female rats at doses up to 325 mg/kg/day PO for 3 days. Based on data from studies TT091033 and TT096025, AUC exposures of suvorexant and M9 were estimated at approximately 40 times and 4 times clinical exposure at the 325 mg/kg dose.

Impurities

The proposed specifications for impurities/degradants in the drug substance/product are below the ICH qualification thresholds, apart from one which has been only partly qualified.

Paediatric use

Since suvorexant is not currently intended for administration to children, nonclinical studies were not performed in which the offspring (juvenile animals) were directly dosed. However, suvorexant is present in the milk of lactating rats. Juvenile rats were indirectly exposed to suvorexant during lactation in the rat postnatal developmental toxicity study.

Nonclinical summary

- Overall, the quality of the nonclinical data was adequate and complied with the necessary ICH guidelines for relevant pivotal studies.
- Suvorexant is a first-in-class, orally active, orexin receptor antagonist. It displayed specific OXR1 and OXR2 binding and antagonist activity *in vitro*, and appropriate modulation of active sleep cycles in animals *in vivo*. Suvorexant metabolites also showed orexin receptor binding and antagonist properties but appear not to penetrate the CNS. Suvorexant and its major human metabolite (M9) showed minimal cross reactivity with common enzymes and receptors.
- Cardiac safety pharmacology studies found reversible inhibition of hERG current at concentrations similar to the clinical C_{max} , but the safety margin is at least 2 orders of magnitude greater for the (very low) unbound drug concentration in human plasma (0.5 to 1.0%). Dog cardiovascular studies *in vivo* were unremarkable, with estimated C_{max} suvorexant exposure 15 times the clinical value.
- Suvorexant demonstrated moderate oral bioavailability with relatively rapid clearance in the main species examined ($t_{1/2}$ 0.8 h rats, 3.8 h dogs). Plasma protein binding was high in all species (96 to 99%), including humans ($\geq 99.5\%$ at plasma C_{max}). Distribution of suvorexant was widespread with no selective association with pigmented tissue. Clearance is mainly by metabolism, with biliary elimination. Metabolism was predominantly oxidative (hydroxylation, bis-hydroxylations, dechlorination) following by glucuronidation, and all human metabolites (including M9) were represented in the animal metabolic profiles (there was no human-specific metabolite). The main metabolic isozyme was CYP3A4, with a lesser contribution from CYP2C19.

- Suvorexant and M9 inhibited CYP3A4 and suvorexant inhibited 2C19 (IC_{50} range 4 to 11 μ M) (human liver microsomes). Suvorexant induced increases in CYP3A12 and 3A26 mRNA (dog hepatocytes), and CYP3A4, 1A2 and 2B6 mRNA (human hepatocytes). Suvorexant was an inhibitor of human intestinal P-gp (IC_{50} 19 μ M) and OCT2 (IC_{50} 1.3 μ M) transporters.
- Apart from clinical signs, the main features of the repeat dose toxicity studies were hypertrophic responses in liver and thyroid (hepatocellular and thyroid hypertrophy in rats, mild hepatocellular hypertrophy in dogs) at the higher doses. In the long term studies, the animal/human exposure (AUC) ratios at the no-effect doses were 3 to 6 (rats) and 6 to 13 (dogs). This liver/thyroid effect, well-known in rats, is attributable to hepatic enzyme induction and is considered not to signal human risk.
- Suvorexant was negative in a series of in vitro and in vivo genotoxicity studies. There were no neoplastic responses in transgenic mice at high (estimated) suvorexant and M9 AUC exposures (\geq 50 times the clinical exposure). Hepatocellular adenomas and thyroid follicular cell adenomas were found in the rat carcinogenicity study at AUC exposures \geq 7 to 11 times clinical exposure (no-effect dose 4 times), with concomitant hepatocellular and thyroid hypertrophy. These responses were attributed to hepatic enzyme induction and increased hepatic thyroxine clearance, supported by a mechanistic (thyroxine clearance) study. This recognised neoplastic response in rats is believed to be of limited relevance to humans.
- An increased incidence of mild retinal atrophy was observed in the rat carcinogenicity study at plasma AUC exposures \geq 7 times clinical AUC (NOEL 4 times clinical exposure). This may represent exacerbation of an age-related change in this species; its clinical relevance is unknown.
- In PO fertility studies in rats, decreases in corpora lutea, implantations and live fetuses were reported at high doses; estimated AUC exposure at the NOEL dose for these effects was 28 times and 15 times clinical exposure in males and females, respectively.
- Suvorexant crossed the placenta in rats and rabbits, and was excreted in rat milk. There was no evidence of teratogenicity in rats and rabbits treated orally with suvorexant during organogenesis, with suvorexant exposures (AUC) approximately 50 times clinical exposure (M9 exposure 2 times in rats and $>$ 30 times in rabbits). Fetal toxicity (weight loss, incomplete ossification) was noted at maternotoxic doses. An oral rat pre/postnatal development study showed only transient body weight reductions in pups (ER $>$ 30); at the no-effect dose, AUC exposure was $>$ 10 times the clinical exposure.
- Limited nonclinical dependence studies (rats, monkeys) did not provide convincing evidence for dependence liability.
- There was some evidence for cataplexy following food enrichment in dogs, with suvorexant and also other orexin receptor antagonists but this was not confirmed in a monkey oral study. The clinical implications of these findings are unclear.

Nonclinical conclusions and recommendation

- The pharmacological studies afforded nonclinical support for the proposed mechanism of action and therapeutic effect of suvorexant.
- In general, the toxicological profile of suvorexant was unremarkable. The main findings were reasonably attributed to hepatic enzyme induction, particularly in rats, leading to hepatocellular and thyroid hypertrophic responses. This mechanism is well-recognised and not considered significant for human risk assessment.

- The clinical significance of the retinal atrophy in rats and cataplexy in dogs is not known.
- There are no nonclinical objections to the registration of suvorexant as proposed by the sponsor.
- Amendments to the draft Product Information document were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

Introduction

Clinical rationale

Insomnia is commonly reported as a symptom. The sponsor argues that '*Chronic insomnia affects about 10% to 30% of the total population (up to one-third of the adult population), with more than 50% of cases experiencing significant daytime consequences such as reduced energy, memory problems, and difficulty concentrating.*' The currently available treatments for insomnia are unsatisfactory because of the problems of tolerance, habituation and abuse. These agents induce sleep through global CNS depression by acting on the neurotransmitter GABA. Hence, there is a need for alternative treatments for insomnia.

Contents of the clinical dossier

The submission contained the following clinical information:

- 32 clinical pharmacology studies, including 25 that provided pharmacokinetic data and 15 that provided pharmacodynamic data.
- One population pharmacokinetic analysis.
- Two pivotal efficacy/safety studies.
- One dose-finding study.
- One long-term (12-month) safety and efficacy study (Protocol 009).
- Additional pooled analyses, Integrated Summary of Efficacy, Integrated Summary of Safety, and a tabulation of pooled safety data.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The sponsor has stated that Good Clinical Practice (GCP) has been conformed to for each of the clinical studies included in the dossier.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 10 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 10. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study P001
		Study P011
		Study P002
	Mass Balance	Study P012
		Study P018
	- Multi-dose	Study P003
	Bioequivalence† - Single dose	Study P007
		Study P041
		Study P051
	Food effect	Study P020
		Study P042
PK in special populations	Target population § - Single dose	Not conducted
	- Multi-dose	Not conducted
	Hepatic impairment	Study P017
	Renal impairment	Study P023
	Neonates/infants/children/adolescents	No data
	Elderly	Study P004
	Elderly	Study P027
	Japanese	Study P005
	Japanese	Study P022
Genetic/gender-	Males vs. females	Study P004

PK topic	Subtopic	Study ID
related PK		
PK interactions	Ketoconazole	Study P008
	Combined Oral Contraceptive	Study P013
	Midazolam	Study P015
	Digoxin	Study P016
	Warfarin	Study P024
	Paroxetine	Study P026
	Rifampin, diltiazem	Study P038
	Ethanol	Study P010
Population PK analyses	Healthy subjects	Report 613

* Indicates the primary aim of the study where applicable.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Suvorexant was well absorbed orally but bioavailability decreased with increasing dose. The mean (5th and 95th percentile) bioavailability for a 10 mg oral dose was 0.82 (0.74 to 0.89), for a 20 mg dose was 0.62 (0.55 to 0.69) for a 40 mg dose was 0.47 (0.41 to 0.53) and for an 80 mg dose was 0.37 (0.31 to 0.42). The clinical trial formulations were bioequivalent to the FMI. The 15 mg and 30 mg dose forms were bioequivalent. The 20 mg and 40 mg dose forms were bioequivalent.

Food did not significantly affect exposure to suvorexant. AUC was similar fasted versus fed, but there was a small increase in C_{max} by food. Suvorexant PKs were not dose-proportional, exposure increases in a less than dose proportional manner with increasing dose. AUC was similar between morning and evening dosing but C_{max} was decreased in the evening.

Time to steady state was approximately 3 days. Suvorexant metabolism was not autoinduced. In the intravenous dose range 5 mg to 30 mg the volume of distribution at steady state (V_{ss}) ranged from 36.5 L to 57.33 L. The plasma protein binding of suvorexant is 99%. The mean (standard deviation (SD)) fraction unbound was 0.77 (0.18) % in subjects with hepatic failure and 1.01 (0.43) % in healthy volunteers. Clearance ranged from 48.60 to 80.62 mL/min and apparent terminal t_{1/2} from 8.9 hours to 13.5 hours. Suvorexant undergoes extensive hepatic metabolism with biliary and renal excretion of its metabolites. The enzymes involved include CYP3A4, CYP2C19 and glucuronidation.

The PK of suvorexant was not significantly altered in either moderate hepatic impairment or severe renal impairment. At 9 hours postdose the plasma concentration in an elderly

subject following a 30 mg dose was observed to be similar to that in a non-elderly subject following a 40 mg dose.

Inhibition of CYP enzymes by ketoconazole increased exposure to suvorexant by more than double. Hence, in combination with drugs that inhibit CYP3A4 and CYP2C19 the dose of suvorexant will need to be reduced. Diltiazem co-administration also increased exposure to suvorexant by more than double (GMR 2.05), albeit to a lesser extent than co-administrated ketoconazole (GMR 2.79).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 11 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 11. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on sleep	Study P003
		Study P011
		Study P005
		Study P002
Secondary Pharmacology	Effect on QTc	Study P022
	Abuse Potential	Study P025
	Effect on Driving Ability	Study P035
		Study P039
	Respiratory Safety: healthy	Study P040
	Respiratory Safety: COPD	Study P031
Gender other genetic and Age-Related Differences in PD Response	Respiratory Safety: OSA	Study P036
	Effect of age	Study P004
PD Interactions	Warfarin	Study P024
	Paroxetine	Study P026
	Ethanol	Study P010

PD Topic	Subtopic	Study ID
Population PD and PK-AE analyses	Phase II/III	Report 615

* Indicates the primary aim of the study if applicable.

‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The time course of single dose suvorexant was examined in four pharmacodynamic (PD) studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg) the effects persisted for up to 24 hours. In a Thorough QTc study at doses up to 240 mg (maximum tolerated) there was no QTc prolongation of regulatory concern. There was lesser abuse potential compared with zolpidem. There was significant next day driving impairment with suvorexant, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion.

Dosage selection for the pivotal studies

Study P006

Study P006 was a multicentre, randomised, double blind, placebo controlled, two period adaptive crossover polysomnography study to evaluate the safety and efficacy of suvorexant in subjects with primary insomnia. The study was conducted at 41 centres from November 2008 to December 2009.

The inclusion criteria included:

- Male or female between 18 and <65 years of age.
- DSM-IV-TR¹² diagnosis of Primary Insomnia based on the investigator's judgment and the patient's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History.
- Completed at least 6 years of formal education; obtains a score 6th grade level on Reading Subtest of Wide Range Achievement Test Version 4 (WRAT-4) at screening, or a comparable measure approved by sponsor.
- Good physical and mental health.
- Total sleep time of ≤6.5 hours on at least 3 out of 7 nights each week within the 4 weeks prior to Visit 1, when not medicated on a hypnotic agent.

¹² The Diagnostic and Statistical Manual of Mental Disorders IV- Text revision (DSM-IV-TR), published by the American Psychiatric Association, offers a common language and standard criteria for the classification of mental disorders.

- Sleep latency of ≥ 30 minutes on at least 3 out of 7 nights each week within the 4 weeks prior to Visit 1, when not medicated on a hypnotic agent.
- ≥ 1 h of wakefulness after sleep onset.
- Spends 6.5 to 9 hours nightly in bed.
- Regular bedtime between 9 PM (21:00) and 12 AM (00:00).
- Willing to refrain from napping.
- Willing to limit alcohol to 2 drinks a day, at least 3 hours before going to bed on non-Polysomnography (PSG) visit days, and refrains from drinking alcohol on all PSG visits and at least 24 hours prior to a PSG visit. (A drink is defined as a 12 ounce bottle/can of beer (approximately 14 grams alcohol) or a 4 ounce glass of wine (approximately 12 grams alcohol) or 1 ounce of liquor (80 proof or 40 % alcohol, approximately 9 grams alcohol)).
- Willing to limit caffeine consumption to 5 standard 6 ounce cups of caffeinated beverages a day, or 600 mg caffeine, avoid caffeine after 4 PM (16:00) on non-PSG nights, and avoid caffeine after 1 PM (13:00) on PSG visits.
- Female patients of reproductive potential are non-pregnant and agree to remain abstinent or to use appropriate double barrier contraception.
- At screening the subject must also have Latency to persistent sleep (LPS) >20 minutes and Wake after sleep onset (WASO) >45 minutes.
- At Baseline the subject has LPS >20 minutes at both Screening and Baseline and a mean WASO ≥ 60 minutes on the combined Screening and Baseline nights, where neither night is ≤ 45 minutes.

The exclusion criteria included:

- History or current evidence of any condition, therapy, lab abnormality or other circumstances that might confound the results of the study.
- History of a neurological disorder, including but not limited to seizure disorder, epilepsy, stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, significant head trauma with sustained loss of consciousness, or classical migraine headaches in the last 10 years.
- History within the past 6 months prior or current evidence of a clinically significant cardiovascular disorder, including, but not limited to: left ventricular hypertrophy, mitral valve prolapse, acute coronary syndrome, unstable angina, congestive heart failure (such as, ejection fraction (EF) $<40\%$), cardiogenic syncope, or symptomatic arrhythmia.
- Electrocardiogram (ECG) clinically significant AV conduction disturbance (such as second or third degree AV block), sick sinus syndrome, bradycardia (resting pulse <40), accessory bypass tract (such as Wolff-Parkinson-White).
- ECG or physical exam a history or current evidence of long QT syndrome, Torsades de pointe or a QTc interval of >450 msec.
- Systolic blood pressure (SBP) >160 mmHg, diastolic blood pressure (DBP) >100 mmHg or pulse rate >100 beats/min.
- Patient is taking, or plans to take, one or more of the following medications (non-inclusive), within the specified washout periods:
 - Clinically relevant CYP3A4 Inhibitors and Inducers: 4 weeks
 - Centrally acting anticholinergics or antihistamines: 2 weeks

- Melatonin: 2 weeks
- Antidepressants: 2 weeks
- Fluoxetine: 4 weeks
- Anxiolytics: 2 weeks
- Benzodiazepines: 2 weeks or 5 t½ lives (whichever is longer)
- Hypnotics: 2 weeks or 5 t½ lives (whichever is longer)
- Any CNS depressants: 2 weeks
- Over-the-counter medications that could affect sleep (e.g., kava-kava, valerian, Benadryl [diphenhydramine] St. John's Wort): 2 weeks
- Stimulants: 2 weeks
- Diet pills: 2 weeks
- Antihistamines (sedating): 2 weeks
- Positive pre study urine drug screen.
- Active Axis I or II disorder as defined in the DSM-IV-TR and as assessed by the Mini International Neuropsychiatric Interview, other than Primary Insomnia.
- Evidence of ongoing depression as determined by a score ≥ 20 on the Quick Inventory of Depressive Symptomatology—Self Report Scale (QIDS-SR16), or scores ≥ 2 on the QIDS-SR16 suicide item #12, or in the judgment of the investigator the patient is impaired, suicidal or otherwise in such a way as to be unable to complete the study procedures in a safe and appropriate fashion.
- History of substance abuse or dependence (including alcohol, marijuana, hypnotics, and drugs of abuse but excludes nicotine dependence).
- History of transmeridian travel (across >3 time zones) or shift work (defined as permanent night shift or rotating day/night shift work) within the past 2 weeks or anticipates needing to travel (across >3 time zones) at any time during the study.
- Consumes the equivalent of >15 cigarettes a day and the Primary Investigator confirms that the patient's sleep disturbance is in part the result of this consumption and the patient is unable to refrain from smoking during the night.
- History of any of following conditions: narcolepsy, cataplexy, circadian rhythm sleep disorder, parasomnia (including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behaviour disorder), sleep-related breathing disorder, periodic limb movement disorder, or restless legs syndrome.
- History of malignancy ≤ 5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Melanoma, leukaemia, lymphoma and myeloproliferative disorders of any duration are excluded.
- History of uncontrolled diabetes as defined by HbA1c of greater than 8%.
- Difficulty sleeping due to a medical condition.
- Body mass index (BMI) >40 kg/m².
- Commenced a weight-loss diet in the past 30 days.
- At screening, an underlying pathology of sleep identified during the screening PSG: Apnoea Hypopnea Index >10 , or >10 periodic leg movements associated with an arousal per h of sleep.

- Positive alcohol breath test as analysed by a breathalyser machine or urine drug screen.

The treatment groups were:

1. Suvorexant 10 mg
2. Suvorexant 20 mg
3. Suvorexant 40 mg
4. Suvorexant 80 mg

Treatments were administered 30 minutes before bedtime on PSG nights and immediately prior to bedtime on non-PSG nights. Subjects were randomised by Interactive Voice Response System (IVRS) to 4 weeks active or with 4 weeks placebo, with crossover to the alternative treatment (active or placebo) following a 1-week single-blind placebo washout between treatment periods.

The primary efficacy outcome measure was Sleep efficiency (SE), derived from Total Sleep Time (TST) from the PSG. The secondary efficacy outcome measures were:

- WASO
- LPS

The exploratory subjective assessments of sleep were:

- Subjective wake after sleep onset (sWASO)
- Subjective time to sleep onset (sTSO)
- Subjective number of awakenings (sNAW)
- Subjective total sleep time (sTST)
- Sheehan Disability Scale
- Insomnia Severity Index

Safety outcome measures were: adverse events (AEs), laboratory safety tests, vital signs, ECG, Tyrer Withdrawal Symptom Questionnaire via the eDiary evening questionnaire, Digit Symbol Substitution Test, and Digit Symbol Copy Test.

A total of 254 subjects were allocated to treatment group: 62 in the suvorexant 10 mg group, 61 in the 20 mg, 59 in the 40 mg and 61 in the 80 mg. Of these, 228 subjects completed the study. There were 148 (58.3%) females, 106 (41.7%) males, and the age range was 18 to 64 years. The treatment groups were similar in demographic characteristics. Morning eDiary compliance was 99.7% and evening diary compliance was 98.3%.

For SE on Night 1, the difference from placebo increased with dose up to the 80 mg dose level (Table 12).

Table 12. Analysis of Sleep Efficiency (SE) (%), Wakefulness after Persistent Sleep Onset (WASO) (minutes) and Latency to Onset of Persistent Sleep (LPS) (minutes) (Full Analysis Set / Data-as-Observed)

Endpoint	Timepoint	Treatment	Diff in LS Means vs. Placebo (SE) [†]	95% CI	p-Value
SE	Night 1	MK4305 10 mg	5.2 (1.71)	(1.9, 8.6)	0.002
		MK4305 20 mg	7.6 (1.72)	(4.2, 11.0)	<.001
		MK4305 40 mg	10.8 (1.72)	(7.4, 14.2)	<.001
		MK4305 80 mg	12.9 (1.73)	(9.5, 16.3)	<.001
	Week 4	MK4305 10 mg	4.7 (1.58)	(1.6, 7.8)	0.003
		MK4305 20 mg	10.4 (1.60)	(7.2, 13.6)	<.001
		MK4305 40 mg	7.8 (1.61)	(4.6, 10.9)	<.001
		MK4305 80 mg	7.6 (1.63)	(4.4, 10.9)	<.001
WASO	Night 1	MK4305 10 mg	-21.2 (6.27)	(-33.5, -8.8)	<.001
		MK4305 20 mg	-24.7 (6.31)	(-37.1, -12.3)	<.001
		MK4305 40 mg	-33.9 (6.33)	(-46.4, -21.5)	<.001
		MK4305 80 mg	-36.8 (6.36)	(-49.4, -24.3)	<.001
	Week 4	MK4305 10 mg	-21.4 (6.45)	(-34.2, -8.7)	0.001
		MK4305 20 mg	-28.1 (6.58)	(-41.0, -15.1)	<.001
		MK4305 40 mg	-33.2 (6.61)	(-46.3, -20.2)	<.001
		MK4305 80 mg	-28.9 (6.70)	(-42.1, -15.7)	<.001
LPS [‡]	Night 1	MK4305 10 mg	-3.4 (6.16)	(-15.6, 8.7)	0.577
		MK4305 20 mg	-9.4 (6.17)	(-21.5, 2.8)	0.130
		MK4305 40 mg	-23.1 (6.20)	(-35.3, -10.9)	<.001
		MK4305 80 mg	-25.4 (6.23)	(-37.7, -13.1)	<.001
	Week 4	MK4305 10 mg	-2.3 (5.00)	(-12.2, 7.5)	0.644
		MK4305 20 mg	-22.3 (5.08)	(-32.3, -12.3)	<.001
		MK4305 40 mg	-3.8 (5.09)	(-13.8, 6.3)	0.459
		MK4305 80 mg	-9.5 (5.17)	(-19.7, 0.7)	0.068

Results based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., multiplied by indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.

[†]Since there was a evidence of a carryover effect for LPS, an analysis of Period 1 LPS data revealed the following differences versus placebo and p-values for Night 1: 10 mg vs. placebo = -19.1 minutes (p-value = 0.020), 20 mg vs. placebo = -17.4 minutes (p-value = 0.030), 40 mg vs. placebo = -31.0 (p-value < 0.001), 80 mg vs. placebo = -22.3 minutes (p-value = 0.007), and the following differences versus placebo and p-values for Week 4: 10 mg vs. placebo = -20.2 minutes (p-value = 0.019), 20 mg vs. placebo = -24.6 minutes (p-value = 0.003), 40 mg vs. placebo = -15.7 (p-value = 0.063), 80 mg vs. placebo = -19.6 minutes (p-value = 0.024)

There was no significant difference between the active treatments. In Week 4, the difference was greatest for the 20 mg dose level, and similar for the 40 mg and 80 mg dose level. While there was no formal pair-wise comparison for WASO, on Night 1 there was a progressive decrease with increasing dose in comparison with placebo, but on Week 4 the greatest decrease was with the 40 mg dose level. For LPS, on Night 1 there was a progressive decrease with increasing dose in comparison with placebo, but this was only significant for the 40 mg and 80 mg dose levels. In Week 4 the only significant decrease compared to placebo was with the 20 mg dose level. There was less effect on LPS on Week 4 than on Night 1 for the 40 mg and 80 mg dose levels.

The results for the exploratory and subjective endpoints are discussed in Attachment 2 Extract from the CER.

Evaluator's overall conclusions on dose selection

Although the data, with the exception of LPS, were supportive of efficacy for the 10 mg dose level, the strongest support was for the 20 mg dose level. For the objective endpoints (PSG): SE supported the 20 mg dose level, WASO supported the 40 mg, and LPS supported the 20 mg dose level. The subjective endpoints were most supportive of the 40 mg dose level, except for the Insomnia Severity Index (ISI) which supported the 20 mg dose level.

Efficacy

Studies providing efficacy data

The current submission contained the following efficacy data:

- Two pivotal efficacy/safety studies.
- One dose-finding study.

- One long-term (12-month) safety and efficacy study.
- Additional pooled analyses, Integrated Summary of Efficacy.

Evaluator's conclusions on efficacy

The efficacy of high dose suvorexant (40 mg for subjects <65 years age and 30 mg for those subjects \geq 65 years age) is supported by the following findings:

- Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 19.7 (11.9 to 27.6) minutes, $p < 0.00001$, sWASO was -6.9 (-11.9 to -2.0) minutes, $p = 0.00565$; and WASO was -22.9 (-30.3, -15.4) minutes, $p < 0.00001$. In Study P029, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 25.1 (16.0 to 34.2) minutes, $p < 0.00001$, sWASO was -8.9 (-14.4 to -3.4) minutes, $p = 0.00167$; and WASO was -29.4 (-36.7 to -22.1) minutes, $p < 0.00001$.
- Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTSO was -8.4 (-12.8 to -4.0) minutes, $p = 0.00019$; and in LPS was -9.4 (-14.6 to -4.3), $p = 0.00037$. In Study P029, at Month 3, the improvement in sTSO was -13.2 (-19.4 to -7.0) minutes, $p = 0.00003$; and in LPS was -3.6 (-10.1 to 2.8), $p = 0.26510$.
- The secondary efficacy outcome measures supported the efficacy of high dose suvorexant.

The efficacy of low dose suvorexant (20 mg for subjects <65 years age and 15 mg for subjects \geq 65 years age) is supported by the following findings:

- In Study P028, sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3 for all endpoints. At Month 3, the improvement in sTST, relative to placebo, was 10.7 (1.9 to 19.5) minutes, $p = 0.01711$; sWASO was -2.4 (-7.9 to 3.1) minutes, $p = 0.38819$; and WASO was -16.6 (-24.8 to -8.3) $p=0.00009$. In Study P029, at Month 3, the improvement in sTST, relative to placebo, was 22.1 (11.5 to 32.6) minutes, $p = 0.00004$; sWASO was -7.7 (-14.1 to -1.3) minutes, $p = 0.01885$; and WASO was -31.1 (-40.1 to -22.2) $p < 0.00001$.
- In Study P028, sleep onset was not improved to the same extent, as for high dose, by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO was approximately 5 minutes and marginally statistically significant: -5.2 (-10.2 to -0.3) minutes, $p = 0.03771$. The improvement in LPS was -8.1 (-13.8 to -2.3), $p = 0.00606$. In Study P029, the improvement in sTSO was -7.6 (-14.7 to -0.4) minutes, $p = 0.03894$. The improvement in LPS was -0.3 (-8.3 to 7.6), $p = 0.93219$.
- The secondary efficacy outcome measures supported efficacy for low dose suvorexant but not as strongly as for high dose.

Efficacy for both high dose and low dose was demonstrated for both the <65 year age group and the \geq 65 year age group. There were no consistent subgroup effects.

The data from Study P028 did not support efficacy beyond three months duration of treatment for either the low dose or high dose treatment. However, the data from Study P009, which was only for the high dose (40 mg for subjects <65 years and 30 mg for subjects \geq 65 years) and which was primarily intended as a long-term safety and tolerability study reported the following at Month 12: the mean (95% CI) improvement in sTST relative to placebo was 27.5 (16.2 to 38.8) minutes $p < 0.0001$, sWASO was -9.7 (-16.5 to -3.0) $p = 0.0048$, and sTSO was -9.7 (-16.5 to -2.9) $p = 0.0055$. There was a small

increase in the subjective quality of sleep in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), $p < 0.0001$; and at Month 12: 0.1 (0.0 to 0.2) $p = 0.0338$. There was a small increase in the subjective refreshed upon waking up in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), $p < 0.0001$; and at Month 12: 0.2 (0.0 to 0.3) $p = 0.0162$. There was an improvement in Insomnia Severity Index that persisted to Month 12: LS mean difference (95% CI) -0.9 (-1.8 to -0.0) $p = 0.0390$. There was an improvement in Clinical Global Impression of Severity (CGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.4 (-0.6 to -0.2) $p = 0.0003$. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) $p < 0.0001$. There was an improvement in Patient Global Impression of Severity (PGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.3 (-0.5 to -0.1) $p = 0.0110$. There was an improvement in Patient Global Impression of Improvement (PGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) $p < 0.0001$.

The subjects included in the pivotal studies (Study P028 and Study P029) did not all have to satisfy PSG criteria. Those subjects in the Questionnaire only cohorts did not undergo PSG in the screening phase and were included in the study on the basis of self-report. Hence, although some of these subjects may not have satisfied the PSG inclusion criteria the results are still generalisable to the intended treatment group. In clinical practice in Australia, few patients presenting with primary insomnia would undergo polysomnography.

The efficacy endpoints used in the clinical trial were appropriate and measured objective endpoints for sleep maintenance and sleep onset. Subjective measures were used for measuring subject wellbeing. The statistical analyses were appropriate and the studies were well powered up to the Month 3 time point.

In the pivotal studies (Study P028 and Study P029) there were substantial improvements in the placebo groups for all the primary efficacy outcome measures over time, from Baseline to Month 3. A dose-response relationship was not demonstrated between low-dose and high-dose suvorexant treatments. Generally, there was also less apparent effect for suvorexant by subjective measures compared to PSG. In Study P029, although at Night 1 there was improvement in sleep onset, there was no apparent benefit at Month 3. These results indicate that the natural history of primary insomnia in the study population was to improve over time and also lend support to the selection of the low dose when initiating treatment.

In addition, the subjective and objective (PSG) endpoints did not show the same responses, which may indicate that these outcome measures were measuring different concepts. Patients may perceive their insomnia differently to how it is measured by polysomnography.

In conclusion, the data support the sponsor's amended dosing recommendations. Although the efficacy data for the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) are not as compelling as for the high dose (40 mg for subjects <65 years age and 30 mg for subjects ≥ 65 years age) there are sufficient data to conclude efficacy. However, the efficacy of the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥ 65 years age) has not been demonstrated for more than 3 months duration. Efficacy has only been demonstrated for primary insomnia and not for any other indication. There are insufficient data to support a 10 mg dose recommendation.

Safety

Studies providing safety data

In the development program for suvorexant there were 32 Phase I studies, one Phase II dose-finding study, two Phase III efficacy studies and one Phase III long term safety study.

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs)
- AEs of particular interest, including behavioural sleep disturbance, residual effects, suicidality, abuse potential, withdrawal effects and tolerance
- Laboratory tests, including serum biochemistry and haematology, ECG test parameters, and vital sign measures (weight, blood pressure, pulse, temperature)
- Suicidal ideation and behaviour assessed by Columbia Suicidality Severity Rating Scale
- Residual effects assessed by Digit Symbol Substitution Test
- Withdrawal assessed by Tyrer Withdrawal Symptom Questionnaire (WSQ)
- Rebound assessed by subjective (sleep diary) and objective (PSG) sleep endpoints

Pivotal studies that assessed safety as a primary outcome

There were two pivotal efficacy/safety studies and one long term safety study included in the submission. Studies P028, P029 and P009 assessed safety as a primary outcome.

Patient exposure

Phase I studies

There were 922 subjects enrolled in the Phase I studies, 842 subjects were exposed to at least one dose of suvorexant, of whom 111 were aged ≥ 65 years. There were 575 (62.4%) males and 347 (37.6%) females. There were 224 subjects exposed to the dose range >40 to 80 mg and 168 exposed to the dose range >80 to 240 mg.

Phase II studies

In Study P006 there were 62 subjects exposed to 10 mg, 62 to 20 mg, 61 to 40 mg and 62 to 80 mg; administered each night for up to 31 days.

Phase III studies

In the combined Phase III population (Study P009, Study P028 and Study P029) there were 2,809 subjects: 1,291 treated with high dose suvorexant, 493 with low dose and 1,025 with placebo. There were 1,744 (62.1%) females, 1,065 (37.9%) males, 1,029 subjects aged 65 to 74 years, and 269 subjects aged ≥ 75 years. There were 500 subjects aged 65 to 74 years and 127 aged ≥ 75 years treated with high dose suvorexant.

In Study P009 there were 521 subjects exposed to suvorexant for up to 434 days. There were 324 subjects exposed to the 30 mg dose and 212 to the 40 mg dose.

In Study P028 there were 637 subjects exposed to suvorexant. There were 225 subjects exposed to suvorexant 40 mg, with 161 exposed for over 3 months and 50 for over 6 months. There were 162 subjects exposed to suvorexant 30 mg, with 115 exposed for over 3 months and 37 for over 6 months. There were 147 subjects exposed to suvorexant 20 mg, with 104 exposed for over 3 months and 20 for over 6 months. There were 107 subjects exposed to suvorexant 15 mg, with 72 exposed for over 3 months and 22 for over 6 months.

In Study P029 there were 626 subjects exposed to suvorexant. There were 233 subjects exposed to suvorexant 40 mg, with 137 exposed for over 3 months. There were 158 subjects exposed to suvorexant 30 mg, with 93 exposed for over 3 months. There were 144 subjects exposed to suvorexant 20 mg, with 68 exposed for over 3 months. There were 95 subjects exposed to suvorexant 15 mg, with 46 exposed for over 3 months.

Postmarketing data

No postmarketing data were included in the submission.

Evaluator's conclusions on safety

The most common treatment-emergent adverse event (TEAE) with suvorexant is somnolence, which in the dose finding study, was reported in one (1.6%) subject with 10 mg, three (4.9%) with 20 mg, six (10.2%) with 40 mg, seven (11.5%) with 80 mg and one (0.4%) with placebo. In Study P028 somnolence occurred in 41 (10.7%) subjects in the high dose group, 13 (5.1%) in the low dose and 13 (3.4%) in the placebo. In Study P029 somnolence occurred in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. In the clinical trials somnolence was commonly attributed to suvorexant.

Sleep paralysis was reported with suvorexant in <1% subjects in Study P028 and Study P029.

Two deaths were reported during the development program: one patient in the placebo group (cerebrovascular accident) and one patient in the suvorexant high-dose group (near-drowning/ hypoxic ischaemic encephalopathy). The latter did not appear related to suvorexant treatment. Serious adverse events (SAEs) were uncommon and did not appear to be related to suvorexant. Discontinuations due to adverse events (DAEs) were also uncommon. There were at least two DAEs related to suicidal ideation. Somnolence and nightmare were more common reasons for DAE in the suvorexant groups.

In the pivotal studies elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were rare, but occurred more commonly with suvorexant. There were no subjects that conformed to Hy's Law.

Renal dysfunction was not associated with suvorexant. Suvorexant was not associated with prolongation of the QT interval, including in a thorough QT study. Clinically significant changes in vital signs were uncommon with suvorexant.

Rebound insomnia appears to be common with suvorexant. In Study P028 rebound by WASO was reported in 29 (34.5%) subjects ceasing high dose, compared to seven (9.1%) continuing; and in 25 (41.0%) subjects ceasing low dose, compared to three (5.0%) continuing.

Withdrawal effects as measured by the Tyrer Withdrawal Score are uncommon, and occur mainly on the first night following ceasing treatment. Suicidal ideation was uncommon with suvorexant. Abuse potential for suvorexant was similar to that for placebo.

There were no clinically significant overdoses during the clinical development program. Hence, the *Effects of suvorexant in overdose* is important missing information.

Although the pharmacodynamic studies indicated significant residual effects, the clinical studies did not indicate an increased risk for traffic accidents or cognitive impairment. In the pharmacodynamic studies the time course of single dose suvorexant was examined in four PD studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with 20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg)

the effects persisted for up to 24 hours. There was lesser abuse potential compared with zolpidem. There was significant next day driving impairment with suvorexant, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects. In Study P009 motor vehicle accidents were slightly more common with suvorexant than placebo: 22 (5.5%) subjects in the suvorexant group and eight (4.1%) in the placebo¹³, but there was no increase in the rate of accidents in Study P028 or Study P029.

The pharmacodynamic studies also investigated sleep safety. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post ingestion.

First round benefit-risk assessment

First round assessment of benefits

The efficacy of high dose suvorexant (40 mg for subjects <65 years age and 30 mg for those subjects ≥65 years age) is supported by the following findings:

- Sleep maintenance was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 19.7 (11.9 to 27.6) minutes, $p < 0.00001$, sWASO was -6.9 (-11.9 to -2.0) minutes, $p = 0.00565$; and WASO was -22.9 (-30.3, -15.4) minutes, $p < 0.00001$. In Study P029, at Month 3, the improvement in sTST, mean (95% CI) relative to placebo, was 25.1 (16.0 to 34.2) minutes, $p < 0.00001$, sWASO was -8.9 (-14.4 to -3.4) minutes, $p = 0.00167$; and WASO was -29.4 (-36.7 to -22.1) minutes, $p < 0.00001$.
- Sleep onset was improved by high dose suvorexant in comparison with placebo through to Month 3. In Study P028, at Month 3, the improvement in sTSO was -8.4 (-12.8 to -4.0) minutes, $p = 0.00019$; and in LPS was -9.4 (-14.6 to -4.3), $p = 0.00037$. In Study P029, at Month 3, the improvement in sTSO was -13.2 (-19.4 to -7.0) minutes, $p = 0.00003$; and in LPS was -3.6 (-10.1 to 2.8), $p = 0.26510$.
- The secondary efficacy outcome measures supported the efficacy of high dose suvorexant.

The efficacy of low dose suvorexant (20 mg for subjects <65 years age and 15 mg for those subjects ≥65 years age) is supported by the following findings:

- In Study P028, sleep maintenance was initially improved by low dose suvorexant in comparison with placebo but the benefit was not sustained through to Month 3 for all endpoints. At Month 3, the improvement in sTST, relative to placebo, was 10.7 (1.9 to 19.5) minutes, $p = 0.01711$; sWASO was -2.4 (-7.9 to 3.1) minutes, $p = 0.38819$; and WASO was -16.6 (-24.8 to -8.3). In Study P029, at Month 3, the improvement in sTST, relative to placebo, was 22.1 (11.5 to 32.6) minutes, $p = 0.00004$; sWASO was -7.7 (-14.1 to -1.3) minutes, $p = 0.01885$; and WASO was -31.1 (-40.1 to -22.2) $p < 0.00001$.
- In Study P028, sleep onset was not improved to the same extent by low dose suvorexant in comparison with placebo through to Month 3. The improvement in sTSO was approximately 5 minutes and marginally statistically significant: -5.2 (-10.2

¹³ Correction: The clinical evaluator has cited the patients in the study population (Treatment phase) who had one or more motor vehicle accidents or violations (MVAV). The number of patients who had motor vehicle accidents were 7 (1.8%) for the suvorexant group and 3 (1.5%) for the placebo treatment.

to -0.3) minutes, $p = 0.03771$. The improvement in LPS was -8.1 (-13.8, -2.3), $p = 0.00606$. In Study P029, the improvement in sTSO was -7.6 (-14.7 to -0.4) minutes, $p = 0.03894$. The improvement in LPS was -0.3 (-8.3 to 7.6), $p = 0.93219$.

- The secondary efficacy outcome measures supported efficacy for low dose suvorexant but not as strongly as for high dose.

Efficacy for both high dose and low dose was demonstrated for both the <65 year age group and the ≥65 year age group. There were no consistent subgroup effects.

The data from Study P028 did not support efficacy beyond three months duration of treatment for either the low dose or high dose treatment. However, the data from Study P009, which was only for the high dose (40 mg for subjects <65 years and 30 mg for subjects ≥65 years) and which was primarily intended as a long-term safety and tolerability study reported the following at Month 12 the mean (95% CI) improvement in sTST relative to placebo was 27.5 (16.2 to 38.8) minutes $p <0.0001$, sWASO was -9.7 (-16.5 to -3.0) $p = 0.0048$, and sTSO was -9.7 (-16.5 to -2.9) $p = 0.0055$. There was a small increase in the subjective quality of sleep in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), $p <0.0001$; and at Month 12: 0.1 (0.0 to 0.2) $p = 0.0338$. There was a small increase in the subjective refreshed upon waking up in the first month: LS mean (95% CI) difference suvorexant-placebo 0.2 (0.1 to 0.2), $p <0.0001$; and at Month 12: 0.2 (0.0 to 0.3) $p = 0.0162$. There was an improvement in Insomnia Severity Index that persisted to Month 12: LS mean difference (95% CI) -0.9 (-1.8 to -0.0) $p = 0.0390$. There was an improvement in Clinical Global Impression of Severity (CGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.4 (-0.6 to -0.2) $p = 0.0003$. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) $p <0.0001$. There was an improvement in Patient Global Impression of Severity (PGI-S) that persisted to Month 12: LS mean difference (95% CI) -0.3 (-0.5 to -0.1) $p = 0.0110$. There was an improvement in Clinical Global Impression of Improvement (CGI-I) that persisted to Month 12: LS mean difference (95% CI) -0.5 (-0.7 to -0.3) $p <0.0001$.

The subjects included in the pivotal studies (Study P028 and Study P029) did not all have to satisfy PSG criteria. Those subjects in the Questionnaire only cohorts did not undergo PSG in the screening phase and were included in the study on the basis of self-report. Hence, although some of these subjects may not have satisfied the PSG inclusion criteria the results are still generalisable to the intended treatment group. In clinical practice in Australia, few patients presenting with primary insomnia would undergo polysomnography.

The efficacy endpoints used in the clinical trial were appropriate and measured objective endpoints for sleep maintenance and sleep onset. Subjective measures were used for measuring subject wellbeing. The statistical analyses were appropriate and the studies were well powered up to the Month 3 time point.

In the pivotal studies (Study P028 and Study P029) for all primary efficacy outcome measures there were substantial improvements in the placebo groups over time, from Baseline to Month 3. There was little apparent dose effect between the high dose and low dose groups, particularly for the PSG endpoints. Generally, there was also less apparent effect for suvorexant by subjective measures compared to PSG. In Study P029, although at Night 1 there was improvement in sleep onset, there was no apparent benefit at Month 3. These results indicate that the natural history of primary insomnia in the study population was to improve over time and also lend support to the selection of the low dose when initiating treatment.

In addition, the subjective and objective (PSG) endpoints did not show the same responses, which may indicate that these outcome measures were measuring different

concepts. Of note, there was discordance between sWASO and WASO. Patients may perceive their insomnia differently to how it is measured by polysomnography.

In conclusion, the data support the sponsor's amended dosing recommendations. Although the efficacy data for the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥65 years age) are not as compelling as for the high dose (40 mg for subjects <65 years age and 30 mg for subjects ≥65 years age) there are sufficient data to conclude efficacy. However, the efficacy of the low dose (20 mg for subjects <65 years age and 15 mg for subjects ≥65 years age) has not been demonstrated for more than 3 months duration. Efficacy has only been demonstrated for primary insomnia and not for any other indication. There are insufficient data to support a 10 mg dose recommendation.

First round assessment of risks

The most common TEAE with suvorexant is somnolence, which in the dose finding study was reported in one (1.6%) subject with 10 mg, three (4.9%) with 20 mg, six (10.2%) with 40 mg, seven (11.5%) with 80 mg, and one (0.4%) with placebo. In Study P028 somnolence occurred in 41 (10.7%) subjects in the high dose group, 13 (5.1%) in the low dose and 13 (3.4%) in the placebo. In Study P029 somnolence occurred in 40 (10.3%) subjects in the high dose group, 20 (8.4%) in the low dose and 12 (3.1%) in the placebo. In the clinical trials somnolence was commonly attributed to suvorexant.

Sleep paralysis was reported with suvorexant in <1% subjects in Study P028 and Study P029.

Two deaths were reported during the development program. Neither appears to have been related to suvorexant (cerebrovascular accident and near-drowning/hypoxic-ischaemic encephalopathy). SAEs were uncommon and did not appear to be related to suvorexant. DAEs were also uncommon. There were at least two DAEs related to suicidal ideation. Somnolence and nightmare were more common reasons for DAE in the suvorexant groups.

In the pivotal studies elevations of ALT and/or AST were rare but occurred more commonly with suvorexant. There was no separate listing of subjects that would have conformed to Hy's Law.

Renal dysfunction was not associated with suvorexant. Suvorexant was not associated with prolongation of the QT interval, including in a thorough QT study. Clinically significant changes in vital signs were uncommon with suvorexant.

Rebound insomnia appears to be common with suvorexant. In Study P028 rebound by WASO was reported in 29 (34.5%) subjects ceasing high dose, compared to seven (9.1%) continuing; and in 25 (41.0%) subjects ceasing low dose, compared to three (5.0%) continuing.

Withdrawal effects as measured by the Tyrer Withdrawal Score are uncommon, and occur mainly on the first night following ceasing treatment. Suicidal ideation was uncommon with suvorexant. Abuse potential for suvorexant was similar to that for placebo. There was also lesser abuse potential compared with zolpidem.

There were no clinically significant overdoses during the clinical development program. Hence, the effects of suvorexant in overdose are important missing information.

Although the pharmacodynamic studies indicated significant residual effects, the clinical studies did not indicate an increased risk for traffic accidents or cognitive impairment. In the pharmacodynamic studies the time course of single dose suvorexant was examined in four PD studies at doses up to 240 mg. There did not appear to be persistence of effect beyond 8 hours for the 10 mg dose level, some persistence for the 20 mg and definite persistence for the 40 mg. The rate of next-day somnolence was estimated to be 7.9% with

20 mg, 10.6% with 40 mg and 14.2% with the 80 mg dose level. At high doses (>100 mg) the effects persisted for up to 24 hours. There was significant next day driving impairment with suvorexant 40 mg in Study P035, similar to that for zopiclone, in non-elderly subjects but no significant impairment in elderly subjects in Study P039. In Study P035 Standard Deviation of Lateral Position (SDLP) was impaired to a similar extent with suvorexant 40 mg compared with zopiclone 7.5 mg but for suvorexant 20 mg SDLP was similar to placebo on Day 9. In Study P039 SDLP was similar to placebo with suvorexant 15 and 30 mg on Days 2 and 9 in the elderly. In Study P009 motor vehicle accidents were slightly more common with suvorexant than placebo: 22 (5.5%) subjects in the suvorexant group and eight (4.1%) in the placebo, but there was no increase in the rate of accidents with suvorexant in Study P028 or Study P029.

The problems with residual effects may be related to the half-life of suvorexant which was estimated to be from 8.9 hours to 13.5 hours. Steady state is achieved at approximately Day 3 of treatment. These PK characteristics are not optimal for a hypnotic and a shorter half-life would be more desirable.

The pharmacodynamic studies also investigated sleep safety. Suvorexant did not impair sleep safety in normal volunteers, subjects with chronic obstructive pulmonary disease or subjects with obstructive sleep apnoea. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post ingestion.

First round assessment of benefit-risk balance

The benefit-risk balance of suvorexant is unfavourable given the proposed usage but would become favourable if the amended dosing recommendations, as stated below, are adopted by the sponsor.

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

Use the lowest dose effective for the patient. The recommended initial dose is 20 mg for non-elderly adults and 15 mg for elderly adults. For patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects, a dose increase to 40 mg for non-elderly adults or 30 mg for elderly adults may be considered.

For use with moderate CYP3A inhibitors:

For non-elderly and elderly patients taking concomitant moderate CYP3A inhibitors, the recommended dose is 15 mg and should not be exceeded.

First round recommendation regarding authorisation

The clinical evaluator is unable to recommend approval of the following indication:

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

The data presented in the submission are supportive of efficacy, at the proposed amended dosing recommendations, for treatment duration of up to 3 months. In addition, all the clinical trials were for primary insomnia, hence this should be reflected in the indication.

The clinical evaluator would have no objection to the approval of suvorexant for the indication:

Belsomra is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Clinical questions

Pharmacokinetics

1. What is the proposed mechanism for the decrease in absolute bioavailability with increasing dose?
2. What is the mechanism of absorption for suvorexant?
3. Is the decreased bioavailability with dose explained by the poor water solubility or is there an active transport process involved in absorption?
4. Does variability in CYP2C19 or UGT alleles affect clearance?

Pharmacodynamics

5. The clinical evaluator does not have any questions relating to pharmacodynamics.

Efficacy

6. The clinical evaluator does not have any questions relating to efficacy.

Safety

7. The sponsor should provide a listing of subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law.

Second round evaluation of clinical data submitted in response to questions

The sponsor has responded to the following questions arising from the clinical evaluation:

Pharmacokinetics

8. What is the proposed mechanism for the decrease in absolute bioavailability with increasing dose?
9. What is the mechanism of absorption for suvorexant?
10. Is the decreased bioavailability with dose explained by the poor water solubility or is there an active transport process involved in absorption?

The sponsor has responded that suvorexant appears to be primarily absorbed by passive diffusion. The sponsor does not expect that active, intestinal uptake by transporters plays an important role in suvorexant absorption. The less than proportional increase in suvorexant exposure observed in the oral dose proportionality Study P018 is believed to be due to solubility limitations.

In the opinion of the clinical evaluator, this response is satisfactory and is consistent with the PK of drugs with similar poor solubility.

11. Does variability in CYP2C19 or UGT alleles affect clearance?

The sponsor has responded that when extrapolating data from in vitro studies '*at the intended clinical doses, the fraction of suvorexant metabolized by CYP2C19 is expected to be less than 20% based on in vitro CYP phenotyping studies (Module 2.6.5.13). Further, as the predominant elimination pathway of suvorexant is oxidative metabolism (refer to Module 2.7.2.2.1.5), UGTs are not involved in the elimination of suvorexant. As a result, variability in CYP2C19 or UGT expression is not expected to impact suvorexant clearance.*'

In the opinion of the clinical evaluator, this response is satisfactory.

12. Please provide a listing of subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law.

The sponsor has responded that there were no subjects with elevations of ALT, AST and bilirubin conforming to Hy's Law in the development program for suvorexant.

In the opinion of the clinical evaluator, this response is satisfactory.

Additional questions from delegate

Comment 1

Results for the primary efficacy endpoint for the low dose versus placebo comparison are exploratory and not controlled for multiplicity effects). The current evidence for efficacy of the proposed revised dose regimen (sponsor's letter dated 17 July) is based on exploratory analyses. Because of this deficiency in the pivotal studies requests the following additional questions:

Please provide a combined analysis of efficacy for Studies P028 and P029 that examines the primary efficacy endpoints for both high dose (HD) and low dose (LD) suvorexant that is,

Maintenance: Change from baseline at Months 1 and 3 for:

- Mean subjective total sleep time (sTSTm) on the daily e-diary
- Wakefulness after persistent sleep onset (WASO) by PSG

Onset: Change from baseline at Months 1 and 3 for:

- Mean subjective time to sleep onset (sTSOm) by daily e-diary
- Latency to persistent sleep (LPS) by PSG

This will be a post hoc analysis. Please provide a statistical plan for this analysis including an assessment of any adjustments performed to account for multiplicity effects.

The sponsor has provided a post hoc analysis of efficacy for the low dose groups using the pooled data from Study P028 and Study P029. Multiplicity was addressed by using a Bonferroni approach to account for the evaluation of the two distinct indications, and there was a hierarchical approach to the hypothesis tests, where the comparison between low dose and placebo must be significant at Month 1 in order to proceed to the comparison at Month 3.

Based on this analysis, there were the following results:

LS mean (95% CI) difference in change from baseline in sTSTm, active – placebo:

- Week 1: 23.7 (19.2 to 28.2) min (p <0.00001) for HD and 15.0 (10.0 to 20.1) min (p <0.0001) for LD
- Month 1: 22.7 (17.2 to 28.2) min (p <0.00001) for HD and 18.4 (12.2 to 24.7) min (p <0.0001) for LD
- Month 3: 22.1 (16.1 to 28.1) min (p <0.00001) for HD and 16.0 (9.2 to 22.8) min (p <0.0001) for LD

LS mean (95% CI) difference in change from baseline in WASO, active – placebo:

- Night 1: -39.9 (-44.4 to -35.4) min (p <0.00001) for HD and -34.6 (-39.8 to -29.3) min (p <0.0001) for LD
- Month 1: -27.6 (-32.7 to -22.6) min (p <0.00001) for HD and -25.4 (-31.3 to -19.5) min (p <0.0001) for LD

- Month 3: -25.9 (-31.2 to -20.7) min (p <0.00001) for HD and -23.1 (-29.2 to -17.0) min (p <0.0001) for LD

LS mean (95% CI) difference in change from baseline in sTSOm, active – placebo:

- Week 1: -9.4 (-12.5 to -6.2) min (p <0.00001) for HD and -6.1 (-9.7 to -2.5) min (p = 0.0081) for LD
- Month 1: -10.1 (-14.0 to -6.3) min (p <0.00001) for HD and -5.6 (-9.9 to -1.2) min (p = 0.01209) for LD
- Month 3: -10.8 (-14.6 to -7.0) min (p <0.00001) for HD and -5.9 (-10.2 to -1.6) min (p = 0.00675) for LD

LS mean (95% CI) difference in change from baseline in LPS, active – placebo:

- Night 1: -15.8 (-19.9 to -11.6) min (p <0.00001) for HD and -11.2 (-16.1 to -6.4) min (p <0.00001) for LD
- Month 1: -11.4 (-15.3 to -7.6) min (p <0.00001) for HD and -9.1 (-13.6 to -4.6) min (p = 0.00007) for LD
- Month 3: -6.4 (-10.5 to -2.3) min (p = 0.00235) for HD and -4.6 (-9.3 to 0.2) min (p = 0.06205) for LD

In the opinion of the clinical evaluator, these data support efficacy for LD suvorexant, and also support the sponsor's proposed approach to dosing. Using LD suvorexant as the starting dose would be expected to minimise adverse effects and still enable those patients who do not achieve a response to have the dose increased to the HD level.

The sponsor also provided a pooled analysis of sTSTM up to the 6 month time point. At the 6 month time point there was loss of effect for suvorexant LD. These data do not support long term use. There was similar loss of effect for suvorexant low dose as measured by sTSOm.

TGA Comment 2

Given the concern expressed by the FDA regarding the effect of the suvorexant high dose regimen on driving ability, are there data on the effect of a 10 mg dose on next day driving ability?

The sponsor responded: 'The sponsor did not evaluate 10 mg of suvorexant in the model on the road driving platform, nor were motor vehicle accidents or violations prospectively assessed at this dose level in insomnia patient studies. However, based on the lack of effects on driving performance at 15 mg and the apparent dose responsiveness of the SDLP measurement, an effect of 10 mg suvorexant on driving performance as measured by SDLP would not be expected.'

In the opinion of the clinical evaluator, this response is satisfactory.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of suvorexant in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of suvorexant in the proposed usage are unchanged from those identified in the first round evaluation.

Second round assessment of benefit-risk balance

As previously stated: the benefit-risk balance of suvorexant is unfavourable given the proposed usage but would become favourable if the amended dosing recommendations, as stated below, are adopted by the sponsor

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

Use the lowest dose effective for the patient. The recommended initial dose is 20 mg for non-elderly adults and 15 mg for elderly adults. For patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects, a dose increase to 40 mg for non-elderly adults or 30 mg for elderly adults may be considered.

For use with moderate CYP3A inhibitors:

For non-elderly and elderly patients taking concomitant moderate CYP3A inhibitors, the recommended dose is 15 mg and should not be exceeded.

The currently available data do not support efficacy for 5 mg and 10 mg dose levels.

Second round recommendation regarding authorisation

The clinical evaluator is unable to recommend approval of the following indication:

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

The data presented in the submission are supportive of efficacy, at the proposed amended dosing recommendations, for treatment duration of up to 3 months. In addition, all the clinical trials were for primary insomnia, hence this should be reflected in the indication.

The clinical evaluator would have no objection to the approval of suvorexant for the indication:

Belsomra is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan RMP Version 1.0 (dated 29 January 2013, Data Lock Point (DLP) 29 November 2012) and Australian Specific Annex (dated 21 February 2013, DLP not given) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 13.

Table 13. Ongoing safety concerns provided by the sponsor in their RMP submission.

Safety Concern	Planned Action(s)
Important Identified Risks	
Residual effects <ul style="list-style-type: none"> • Somnolence • Impairment when driving or operating heavy machinery 	Routine Pharmacovigilance
Additive impairment with concomitant use of EtOH	Routine Pharmacovigilance
Important Potential Risks	
Additive impairment with concomitant use of CNS depressants	Routine Pharmacovigilance
Cataplexy (pharmacologically mediated)	Routine Pharmacovigilance
Suicidal Ideation and/or behaviors/Worsening of Depression	Routine Pharmacovigilance
Complex sleep-related behaviors	Routine Pharmacovigilance
Abuse potential	Routine Pharmacovigilance
Important Missing Information	
Pregnancy and lactation	Routine Pharmacovigilance
Populations insufficiently studied/ not studied: <ul style="list-style-type: none"> • Pediatric patients • All non-insomnia sleep disorders, including narcolepsy • Severe COPD, severe OSA • Severe hepatic insufficiency 	Routine Pharmacovigilance

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes only routine pharmacovigilance activities for important identified and potential risks and missing information (see table above).

Risk minimisation activities

The sponsor has proposed routine risk minimisation activities and states the following with regard to additional risk minimisation activities:

'The safety profile of suvorexant has been adequately evaluated in clinical experience from studies, and the important safety concerns have been characterized. As suvorexant is a hypnotic, and as such may be subject to local regulatory requirements, it will be licensed and prescribed in accordance with local requirements for these products. Based on the available data for this product, routine risk minimization through the proposed prescribing information is sufficient, and no additional risk minimization is necessary.'

Reconciliation of issues outlined in the RMP report

The following is a summary of the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation 1 in RMP evaluation report

Sleep paralysis' should be added as an Important Potential Risk.

Sponsor's response (or summary of the response)

'Although the Sponsor does not consider sleep paralysis to be an important medical risk, it may be of significant concern to patients and may alter the personal benefit/risk assessment for any individual patient. Therefore, the sponsor agrees to add sleep paralysis to Important Potential Risks in the RMP. The sponsor provides information below regarding sleep paralysis for consideration by the TGA.

For perspective, sleep paralysis is common in the general population with a lifetime prevalence of 7.6%. Sleep paralysis has been associated with common sleep conditions/disturbance (for example, sleep deprivation, sleep disorders, jet lag, and shift work). Sleep paralysis has also been linked to medical conditions including narcolepsy, hypertension, and seizure disorders. In clinical practice, sleep paralysis is treated using patient education, and does not require pharmacologic or behavioural intervention.

In the Phase III clinical program, the incidence of sleep paralysis was low. In patients treated for up to 3 months, the incidence of sleep paralysis was 0.2% (n=1) for suvorexant 15/20 mg, 0.3% (n=4) for suvorexant 30/40 mg, and 0% for placebo. One additional event occurred in a patient treated with suvorexant 30/40 mg beyond 3 months. The majority of these occurrences was fleeting, mild to moderate in severity, and did not recur while continuing on study drug. One patient on suvorexant 30/40 mg discontinued due to sleep paralysis.

In summary, isolated cases of sleep paralysis in the suvorexant program were rare and did not recur. Therefore, as stated above, the sponsor agrees to add sleep paralysis to Important Potential Risks in the RMP.'

OPR evaluator's comment

This is considered acceptable.

Recommendation 2 in RMP evaluation report

Effects of suvorexant in overdose' should be added as Important Missing Information.

Sponsor's response (or summary of the response)

The sponsor will add 'effects in overdose' to Important Missing Information in the RMP. Information on the management of overdose is currently included in the proposed PI. A summary of information on overdose in the suvorexant program is provided in the Integrated Summary of Safety (ISS) in the initial submission. The sponsor provides a summary of information related to overdose for perspective below.

In the suvorexant development program, an overdose was defined as ingestion of a dose of study medication (accidental or intentional) exceeding the specified dose to be administered nightly in each protocol. Reporting was based on patient report; therefore, an AE of 'overdose' was only reported when a patient reported taking more medication than prescribed. Relatively few overdoses were reported in the suvorexant development program and the numbers/proportion of events were higher for placebo than for suvorexant. During the treatment phase and extension phase for the Phase III trials, 11 patients treated with suvorexant (9 in the suvorexant 30/40 mg group (0.7%) and 2 patients in the suvorexant 15/20 mg group (0.4%)) and 10 patients in the placebo group reported overdose (1.0 %). There were no reports of intentional overdose in the suvorexant development program and no other AEs were associated with the overdoses. In the clinical pharmacology studies, one subject (in the COPD Study; P032) was accidentally overdosed by the study site, and received 280 mg total exposure on a single evening. Study procedures were followed as per protocol during the night. The subject did not report any AEs or have other complications following the overdose or upon awakening the following morning. When the subject was informed of the overdose he reported he was tired.

General medical practice recommends that in cases of possible overdose where medical treatment is deemed appropriate, gastric lavage with supportive care is recommended; however, no data for these interventions are available for suvorexant. The value of dialysis in the treatment of overdosage with suvorexant has not been determined. As suvorexant is highly protein bound, haemodialysis is not expected to contribute to elimination of suvorexant.

In multiple Phase I studies during the suvorexant clinical development program where subjects were administered doses several fold over those recommended for the treatment of insomnia, the effects observed were predictably related to the intended effect of the drug and consisted primarily of somnolence, which resolved without the need for any medical intervention. As noted above, the sponsor will add 'effects in overdose' to Important Missing Information in the RMP.'

OPR evaluator's comment

This is considered acceptable.

Recommendation 3 in RMP evaluation report

The sponsor should provide details on whether the following populations were studied sufficiently, and if not, the sponsor should add these populations as Important Missing Information: patients with anxiety; patients with depression (clinically diagnosed depression rather than depression symptoms); patients with a history of substance abuse.

Sponsor's response (or summary of the response)

'Please note that precautions regarding prescribing suvorexant to patients with depression and patients with a history of drug abuse are currently included in the proposed PI. The sponsor acknowledges limited data in the clinical development program in patients with clinically diagnosed depression and in patients with a history of drug abuse, and agrees to add 'patients with clinically diagnosed depression' and 'patients with a history of substance abuse' to Important Missing Information in the RMP. However, given the overlap between anxiety symptoms and insomnia, the sponsor believes that the efficacy and safety results obtained in patients with primary insomnia can be generalized to patients with insomnia and anxiety disorders and that patients with anxiety do not constitute Important Missing Information.'

In order to better contextualise the sponsor's response to this request, the sponsor wishes to put forward the data that are available on these populations from Phase I and Phase III trials.

For Phase I studies, based on inclusion and exclusion criteria, healthy subjects were enrolled and subjects with anxiety, depression or a history of substance abuse were generally excluded. In the dedicated abuse liability study, 36 male and female recreational polydrug users with a history of sedative/hypnotic and psychedelic drug abuse were enrolled into the treatment phase, which included suvorexant (P025).

In the confirmatory efficacy trials (P028 and P029), patients with evidence of ongoing major depression (per the Mini International Neuropsychiatric Interview), or significant depressive symptoms (that is, Quick Inventory of Depression Symptomatology score ≥ 20) and patients treated with psychotropic medications (including antidepressants and anxiolytic drugs) were excluded from the trial.

In P009, the long term safety trial, inclusion criteria were less restrictive. Patients with ongoing psychiatric diagnoses were to be excluded if the condition interfered with ability to participate in the trial (investigator's opinion) or if they required treatment with prohibited medications (some antidepressants such as MAOI and tricyclic antidepressants and anxiolytics (benzodiazepines and non- benzodiazepines) were prohibited).

Patients with a history of or current substance abuse (unless in remission for at least 1 year) were excluded from all Phase II and 3 trials.

Number of patients with specific psychiatric conditions in the Phase III program

Due to the chronic and recurrent nature of these psychiatric conditions, patients with prior history are at greater risk of developing a future episode. The Phase III data were thereby reviewed to define the subset of patients reporting a medical history of depression, anxiety, and/or substance abuse, including both those with a past history as well as those reporting a current condition at the time of screening. Review of conditions reported at screening related to anxiety, depression, or substance abuse in Phase III trials identified the following conditions for depression: depressed mood, depression, depressive symptom, dysthymic disorder, major depression, mood swings, seasonal affective disorder, suicidal ideation, and suicide attempt; for anxiety: anxiety, anxiety disorder, generalized anxiety disorder, limited symptom panic attack, panic attack, panic disorder, post-traumatic stress disorder, social avoidant behavior, and social phobia; and for substance abuse: alcohol abuse, alcoholism, and nicotine dependence.

The table below (Table 14) presents the number (%) of patients in the Phase III trials who reported a history (past or currently) of depression, anxiety, and/or a substance use disorder by protocol and treatment group. Overall, the prevalence of these conditions by history was low: 2.1% (58/2809) reported anxiety, 3.2% (90/2809) reported depression, representing 140 unique patients reporting anxiety and/or depression (8 patients reported comorbid anxiety and depression). A prior history of a substance use disorder was reported by very few patients, 7 of 2809 (0.2%); this low incidence was due to the exclusion of this patient population per the design of the protocols (that is, exclusion of patients with a history of substance abuse with less than 1 year of remission).

Table 14. Number and percentage of patients in the Phase III trials reporting depression, anxiety, and/or substance use disorder by medical history P028, P029, P009

Medical History	Protocol	Suvorexant 15/20 mg			Suvorexant 30/40 mg			Placebo		
		n	N	%	n	N	%	n	N	%
Anxiety	009				18	521	3.5	13	258	5
	028	3	254	1.2	3	383	0.8	6	384	1.6
	029	3	239	1.3	7	387	1.8	5	383	1.3
	Total	6	493	1.2	28	1291	2.2	24	1025	2.3
Depression	009				31	521	6	22	258	8.5
	028	6	254	2.4	7	383	1.8	5	384	1.3
	029	1	239	0.4	8	387	2.1	10	383	2.6
	Total	7	493	1.4	46	1291	3.6	37	1025	3.6
Anxiety or Depression	009				42	521	8.1	30	258	11.6
	028	8	254	3.1	10	383	2.6	10	384	2.6
	029	3	239	1.3	14	387	3.6	15	383	3.9
	Total	11	493	2.2	66	1291	5.1	55	1025	5.4
Substance use disorder	009				2	521	0.4	1	258	0.4
	028	1	254	0.4	2	383	0.5	0	384	0
	029	0	239	0	1	387	0.3	0	383	0
	Total	1	493	0.2	5	1291	0.4	1	1025	0.1

Depressive symptoms were also evaluated at screening in the Phase III trials using the Quick Inventory of Depressive Symptomatology (QIDS). As expected, the proportion of patients presenting with at least clinically moderate symptoms of depression (defined as a total score of 10 or more) was higher than the proportion of patients with a history of depression. Of 2807 patients in the Phase III trials for whom QIDS data were available at screening, 171 (6.1%) patients had initial QIDS scores of 10 or greater, including 43 (8.7%) patients in the suvorexant 15/20 mg group, 66 (5.1%) patients in the suvorexant 30/40 mg group, and 62 (6.0%) patients in the placebo group.

Overall, while the prevalence of comorbid psychiatric conditions in the Phase III population was low, a substantial proportion of the Phase III patient population had other comorbid disorders. Overall, 68 to 70% of the patients in the combined P028 and P029

population and 85 to 87% of patients in P009 had active co-existing medical conditions based on the patient-reported medical history.

Summary

The safety of suvorexant at doses up to 40 mg has been studied extensively in patients with insomnia with or without other co-morbid conditions. Despite intention to enrol patients with 'primary insomnia', there is an evolving perspective that this is a condition that rarely occurs in isolation, and in acknowledgement of this the term has been dropped from use in Diagnostic and Statistical Manual of Mental Disorder, 5th edition (DSM-V).

While the sponsor acknowledges that the safety of suvorexant in patients with depression or substance use history was not systematically evaluated, the overall safety profile observed in patients treated with suvorexant across a substantial clinical program in patients with concurrent mixed medical histories, many of whom were elderly, suggests that the likely risks associated with the use of suvorexant have been identified, and these risks can be addressed in product labelling. Nonetheless, the sponsor acknowledges limited data in the clinical development program in patients with clinically diagnosed depression and a history of substance abuse, and agrees to add these patient populations to Important Missing Information in the RMP.

Lastly, it may be helpful to also mention that while the aetiology of insomnia is not well understood, psychophysiological factors such as stress and anxiety (including hyperarousal as a symptom of anxiety) are thought to play a major role in causing sleep disturbances. With regard to anxiety, patients with insomnia are up to 17 times more likely to have clinically significant anxiety than those without insomnia. In addition, anxiety frequently precedes the development of insomnia, particularly in individuals without a history of an anxiety disorder. In the Phase III clinical program, the prevalence of a prior history of an anxiety disorder diagnosis was low; however, it is likely that the presence of anxiety symptoms was not uncommon in this patient population (that is, insomnia associated with hyperarousal). Given these considerations of overlap between anxiety symptoms and insomnia, the sponsor believes that the efficacy and safety results obtained in patients with primary insomnia (by DSM-IV criteria) can be generalized to patients with insomnia and anxiety disorders and that patients with anxiety do not constitute Important Missing Information. Considerations related to the use of suvorexant in individuals taking other medicines that produce CNS depressant effects is included in the proposed PI.

OPR evaluator's comment

The sponsor's inclusion of these populations as Important Missing Information is considered acceptable.

Recommendation 4 in RMP evaluation report

The sponsor should consider conducting additional pharmacovigilance activities to address residual effects further, particularly effects on driving and operating machinery.

Sponsor's response (or summary of the response)

The sponsor has conducted a thorough and extensive evaluation of residual effects following the use of suvorexant, particularly with regards to driving. The CSRs for these studies are contained within the submission and are summarized below. For a comprehensive summary of residual effects, please refer to the Integrated Summary of Safety in the submission. Please note that precautions regarding residual effects are included in the proposed PI. In addition, the sponsor proposes to implement an event-specific questionnaire for the purpose of supplementing standard post approval surveillance for motor vehicle accidents. An event-specific questionnaire will be developed with input from external experts. The questionnaire will be automatically sent out from our case processing department upon receipt of any report containing predefined terms

that reflect the events of interest. The questionnaire will be sent to the original reporter, requesting additional information as defined in the questionnaire. Completed questionnaires will be processed as updates to the original reports, adding all additional information received. This will provide additional information around these events of interest, allowing further and more complete characterization of these events.

Assessment of residual effects in the suvorexant clinical development program

The comprehensive evaluation of potential residual effects of suvorexant included objective and subjective measurements across the clinical development program in both non-elderly (age 18-64) and elderly (age ≥ 65) age groups, as summarized in the table below (Table 15). Objective evaluation included assessments of memory, balance, psychomotor performance, and driving performance in Phase I studies; and assessment of psychomotor performance using the Digit Symbol Substitution Test (DSST) in the Phase IIb/III studies. The DSST was performed in the morning 30 minutes to an hour after the patient awoke following completion of the overnight PSG assessment, approximately 8.5 to 9 hours after study medication was administered. In the insomnia trials, next-day residual effects were also characterized through review of selected spontaneously reported adverse events that were characterized as possibly associated with residual effects. In addition, occurrences of motor accidents and/or traffic violations (when the patient was a driver) and any associated adverse events were prospectively assessed at each visit using a specific questionnaire completed by the patient in the Phase III trials.

Table 15. Residual effect assessments in the suvorexant program

	Phase 1	Phase 2	Phase 3
Adverse events	✓	✓	✓
<i>Memory and balance</i>			
Word learning test	✓		
Body sway test	✓		
Adverse events of falls	✓	✓	✓
<i>Next-day performance</i>			
Psychomotor performance			
Digit symbol substitution test	✓	✓	✓
Digit symbol copy test		✓	
Simple reaction time	✓		
Choice reaction time	✓		
<i>Driving performance</i>			
Highway driving studies	✓		
Motor vehicle accidents and Violations			✓

To facilitate collection of detailed information on selected cases of next day somnolence, excessive daytime sleepiness (EDS) was designated as a pre-specified event of clinical interest (ECI) in the program. EDS in this context was predefined as a form of recurrent and/or persistent residual somnolence beyond the more typical short-lived next-day somnolence indicative of potential drug carryover effect. Note that as defined for this program, the EDS designation is an operational definition for the purpose of detailed adverse event data collection, but is not synonymous with the clinical diagnostic syndrome of Excessive Daytime Sleepiness seen in conditions such as obstructive sleep apnoea, narcolepsy, or shift work disorder. In the latter circumstance, EDS symptoms result from and are sustained by the underlying disorder and may require medical intervention. In the suvorexant program, the symptoms of sleepiness are likely directly related to the transient pharmacology of the drug and symptoms are likely to abate spontaneously while continuing therapy or upon discontinuation of therapy, without need for medical intervention.

In addition, investigation of PK/PD relationships for next day residual effects associated with the suvorexant use in the Phase II and III studies was conducted using both the objective Digit Symbol Substitution Test (DSST) data and the subjective spontaneously reported AE data. The findings of various evaluations to assess residual effects are summarized below.

Results

Adverse events

In the Phase III program in patients with insomnia, somnolence was the most commonly reported adverse event reported and was dose-related. In patients treated for up to 3 months, the incidence of somnolence for suvorexant 15/20 mg, suvorexant 30/40 mg, and placebo was 6.7%, 10.7%, and 3.0%, respectively. Somnolence was reported as mild-to-moderate in the majority of occurrences, with onset generally within the first week after initiating treatment, and resolved spontaneously without medication interruption, with few events of somnolence reported after one month of treatment. Discontinuation due to somnolence was uncommon: 0.2% (n=1), 1.7% (n=22), and 0.3% (n=3) for suvorexant 15/20 mg, suvorexant 30/40 mg, and placebo, respectively. Examination of residual effects AEs by age subgroup revealed that results were generally comparable to the overall population.

The reported next day somnolence on suvorexant is comparable to other modern hypnotics, including shorter-acting drugs that have less pronounced effects on sleep maintenance. The table below (Table 16) summarises the frequency of somnolence by patients taking suvorexant (Kaplan-Meier estimates from pooled Phase III data), compared with frequency of somnolence from zolpidem CR and eszopiclone (data from Ambien CR and Lunesta package inserts).

Table 16. Reported next day somnolence on suvorexant is comparable to other modern hypnotics

	Somnolence (Increase above placebo non-elderly, self-report)	
	Lower dose (noted in parentheses)	Higher dose (noted in parentheses)
3-week Estimate		
Suvorexant [†] (20 mg, 40 mg)	5%	8%
Zolpidem CR [§] (N/A, 12.5 mg)	N/A	13%
6-week Estimate		
Suvorexant [†] (20 mg, 40 mg)	5%	9%
Eszopiclone [‡] (2 mg, 3 mg)	7%	5%

[†] Kaplan-Meier estimates from pooled Phase 3 data
[‡] Data from Lunesta® (eszopiclone) package insert
[§] Data from Ambien CR® (zolpidem tartrate extended-release) package insert

The incidence of excessive daytime sleepiness (EDS), a subset of somnolence, was low overall in the first 3 months of treatment, with slightly more reports among patients treated with suvorexant 30/40 mg (1.1% ; n=14) than for placebo (0.2%; n=2) and suvorexant 15/20 mg (0.6%; n=3). In those patients who experienced EDS, onset generally occurred during the first week of treatment. For patients taking suvorexant, the intensity of EDS was mild in 25% of cases (2 on suvorexant 15/20 mg, 2 on suvorexant 30/40 mg, 1

on placebo), moderate in 50% of cases (1 on suvorexant 15/20 mg, 7 on suvorexant 30/40 mg, 1 on placebo) and severe in 25% of cases (5 on suvorexant 30/40 mg only). In the first 3 months of treatment, 11 of 17 patients on suvorexant (most taking suvorexant 30/40 mg) discontinued due to the EDS; with symptoms resolving following treatment discontinuation. With continued treatment up to 12 months, 6 additional patients on suvorexant 30/40 mg (1.5% total) reported EDS (compared to 1 on placebo (0.3% total) and none on suvorexant 15/20 mg); of these, four discontinued treatment due to EDS. Analysis and counts of excessive daytime sleepiness for 0-6 months and 0 to 12 months is provided in the initial submission.

In summary, only a small minority of patients reported somnolence or other adverse events suggestive of residual effects in the suvorexant Phase III program, and among these few had symptoms severe or persistent enough to require stopping treatment.

As summarised in the letter to the Delegate on 17 July 2013, the sponsor's updated Dosage and Administration is for the low suvorexant dose to be the starting dose: 15 mg elderly/20 mg nonelderly. Patients who report an inadequate response with suvorexant 15/20 mg after initial treatment are unlikely to receive significant additional benefit with continued treatment at the same dose. Similarly, patients who do not experience somnolence early are unlikely to experience somnolence later. Therefore, to achieve the most positive benefit-to-risk by increasing efficacy while minimizing residual effects, a dose increase to 30 mg for elderly or 40 mg for non-elderly adults may be considered for those patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects. For most patients, the most important adverse events affecting tolerability will be those related to next-day somnolence, which can be easily monitored and managed clinically. Importantly, excluding patients who experience problems tolerating the lower dose from those considered for a dose increase will also serve to reduce the risk of such events at the high dose, as those patients most sensitive to next-day effects at the low dose will not be exposed to the high dose, where they may be likely to experience more pronounced effects.

In Phase I, potential residual effects were evaluated in the morning after night-time administration of suvorexant using tests of memory (immediate and delayed word recall) and balance in four double-blind studies (N = 103), and psychomotor performance (DSST +/- simple and choice reaction time) in 5 double-blind studies (N=125). Overall, there was no consistent evidence of significant residual effects at therapeutic doses of suvorexant as assessed by these tests. In one of the five studies (P035, non-elderly driving study), statistically significant next-day effects were observed on some endpoints (DSST and delayed word recall after a 40 mg single dose, and body sway after a single 20 mg or 40 mg dose, without impairment after multiple doses). However, there were no significant effects on these endpoints in the other studies.

Patients in the Phase III confirmatory efficacy studies completed the DSST in the morning following overnight PSG assessments (N=1493), approximately 9 hours post dose. A small increase in the mean number of correct items compared to baseline, indicating improvement in performance, was observed with both suvorexant and placebo with repeated measures, consistent with the established learning effect seen with this assessment. Comparing suvorexant to placebo, no differences were observed to suggest next-day impairment in psychomotor performance based on DSST on the morning following acute treatment with suvorexant (Night 1) or at subsequent time points (Months 1 and 3) in patients treated with suvorexant for up to 3 months; see Table 17 (below). In elderly patients, the degree of improvement for DSST on Night 1 was greater for those on placebo compared to those taking suvorexant. However, the magnitude of the difference observed (approximately 2 items) was small, and this difference was not observed at subsequent assessments at the Month 1 or Month 3 assessments, and is therefore likely

not clinically meaningful. DSST results for the non-elderly patients were similar to those for the overall population.

Table 17. Analysis of digit symbol substitution test number of correct responses by time point combined Phase III population: 0-3 months. All patients as treated-PQ cohort/Data-as-observed

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline at Time Point	
				Mean (SD)	LS Mean (95% CI) [†]
Night 1					
Suvo 15/20mg	338	50.8 (14.7)	52.7 (15.4)	1.9 (8.9)	1.6 (0.8, 2.5)
Suvo 30/40mg	577	52.8 (17.2)	54.1 (16.8)	1.3 (8.6)	1.5 (0.8, 2.1)
Placebo	578	51.7 (15.9)	54.1 (15.7)	2.4 (8.3)	2.3 (1.7, 3.0)
Month 1					
Suvo 15/20mg	321	51.1 (14.4)	53.1 (16.2)	2.0 (10.5)	1.8 (0.8, 2.8)
Suvo 30/40mg	560	52.7 (16.7)	54.4 (16.6)	1.7 (10.4)	1.9 (1.1, 2.7)
Placebo	551	51.8 (15.9)	54.0 (15.5)	2.2 (9.0)	2.2 (1.4, 2.9)
Month 3					
Suvo 15/20mg	307	50.8 (14.1)	53.5 (14.7)	2.7 (8.6)	2.4 (1.3, 3.4)
Suvo 30/40mg	526	53.0 (16.9)	54.9 (16.9)	1.9 (10.7)	2.1 (1.3, 2.9)
Placebo	516	51.7 (15.8)	54.7 (15.9)	3.0 (9.9)	2.9 (2.1, 3.7)
Pairwise Comparison		Difference in LS Means (95% CI) [†]			
Night 1					
Suvo 30/40mg vs. Placebo		-0.9 (-1.8, 0.1)			
Suvo 15/20mg vs. Placebo		-0.7 (-1.8, 0.4)			
Month 1					
Suvo 30/40mg vs. Placebo		-0.3 (-1.4, 0.8)			
Suvo 15/20mg vs. Placebo		-0.4 (-1.7, 0.9)			
Month 3					
Suvo 30/40mg vs. Placebo		-0.8 (-1.9, 0.3)			
Suvo 15/20mg vs. Placebo		-0.5 (-1.9, 0.8)			

[†] Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates.

Suvo 15/20mg = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Suvo 30/40mg = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Exposure-response modelling of next day residual effects from pooled Phase II and III data was conducted for the objective measure Digit Symbol Substitution Test (DSST) and spontaneously reported next day residual effects of somnolence and fatigue (any occurrence including short duration and mild severity). Next day residual effects were related to suvorexant concentration in the morning (9 hours post dose -C9hr). The DSST exposure-response relationship was best characterized by a linear C9hr-response drug model with a shallow slope that increased modestly in elderly relative to non-elderly. Somnolence incidence rates with C9hr gradually increase in incidence across the clinical exposure range. Fatigue incidence versus C9hr was well described by a bi-phasic model, consistent with the incidence of fatigue initially increasing with increasing C9hr, but then falling at higher C9hr values. Notably the elderly were not found to be more sensitive to somnolence or fatigue than non-elderly. EDS-C9hr relationship was explored graphically and the results suggest a gradually increasing trend with C9hr. Dose simulations using these exposure-response models support that DSST changes (for example, a >3 decrease in number correct) are unlikely at high doses in Phase III for both non-elderly and elderly, and that most patients will not experience residual effects (for example, somnolence, fatigue) at the recommended clinical doses although there is a modest exposure-dependency

Effects on ability to drive or operate machinery

Phase I

In order to further evaluate the residual effect profile, a model on-the-road driving platform was used to assess driving performance in the morning 9 hours after night-time administration of suvorexant. Next-day driving performance was assessed with this platform in two studies, in non-elderly subjects (23 to 64 years, P035) and elderly subjects (≥65 years, P039), and both studies included driving assessments after single doses and multiple doses, and at 15/20 mg and 30/40 mg of suvorexant.

Both studies had a similar design: randomized, double-blind, placebo- and positive-controlled, 4-period crossover studies. Zopiclone 7.5 mg, administered double-blind as a single dose on Day 1 and again on Day 8, was included as an active control. The primary endpoint was standard deviation of lane position (SDLP), a measure of road tracking error or 'weaving' on Day 2 (after a first, that is, single dose) and Day 9 (after 8 consecutive doses). A mean increase in SDLP of 2.4 cm or greater compared to placebo is generally considered clinically meaningful, based on literature data indicating a blood alcohol concentration of 0.05% on average increases SDLP by 2.4 cm. The primary hypothesis in both studies was that there is no clinically meaningful mean increase on SDLP (supported if the 90% CI for the mean difference from placebo lay below 2.4 cm for suvorexant 15/20 mg and 30/40 mg, on both Day 2 and on Day 9). In addition to the primary analysis comparing SDLP treatment means, a "symmetry analysis" was performed to determine if there was a statistically significant difference in the number of subjects with an increase in SDLP from placebo ≥ 2.4 cm (worsening) versus the number of subjects who had a difference in SDLP ≤ -2.4 cm (improvement).

Results

In both studies, zopiclone demonstrated assay sensitivity as assessed by the mean analysis. Further, the symmetry analyses also showed significant effects of zopiclone at all the time points. In the elderly subjects, there was no clinically meaningful impairment of next-day driving performance at either dose level of suvorexant (15 mg or 30 mg) as assessed by the mean and symmetry analyses of SDLP (Figure 2, Table 18). In the non-elderly subjects, there was no clinically meaningful impairment of next-day driving performance at either dose level based on the primary endpoint (Figure 2), since the 90% confidence intervals for the mean SDLP treatment differences were < 2.4 cm at both dose levels. The symmetry analysis of SDLP revealed a statistically significant greater number of subjects with SDLP treatment differences of ≥ 2.4 cm (suggestive of impairment) than those with SDLP differences ≤ -2.4 cm on Day 2 for 20 mg and 40 mg and on Day 9 for 40 mg of suvorexant (Table 19).

Figure 2. SDLP difference from placebo (mean \pm 90% CI) (cm) following single dose (Day 2) and multiple dose (Day 9) of suvorexant in healthy non-elderly and elderly subjects (vertical dotted line at 2.4 cm indicates the pre specified clinical significance bound)

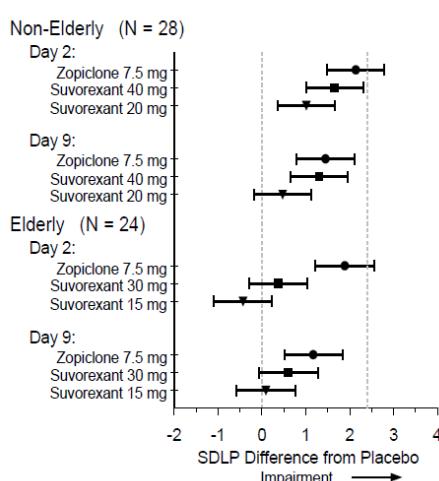


Table 18. Results of symmetry analysis for individual SDLP difference (active-placebo) following PM administration of suvorexant 15 mg, 30 mg single dose (Day 2) and multiple doses (Day 9) and single dose of zopiclone 7.5 mg (Day 2 and Day 9) in elderly subjects (N=24)

	Day=2			Day=9		
	MK-4305 15 mg	MK-4305 30 mg	Zopiclone 7.5 mg	MK-4305 15 mg	MK-4305 30 mg	Zopiclone 7.5 mg
Number of subjects with Δ SDLP \geq 2.4 cm	0	3	8	0	5	6
Number of subjects with Δ SDLP \leq -2.4 cm	3	1	0	0	1	1
Statistically Significant Asymmetry	No	No	Yes	No	No	Yes

Table 19. Results of symmetry analysis for individual SDLP difference (active-placebo) following PM administration of suvorexant 20 mg, 40 mg single dose (Day 2) and multiple doses (Day 9) and single dose of zopiclone 7.5 mg (Day 2 and Day 9) in non-elderly subjects (N=28)

	Day=2			Day=9		
	MK-4305 20 mg	MK-4305 40 mg	Zopiclone 7.5 mg	MK-4305 20 mg	MK-4305 40 mg	Zopiclone 7.5 mg
Number of subjects with Δ SDLP \geq 2.4 cm	6	11	15	3	6	8
Number of subjects with Δ SDLP \leq -2.4 cm	0	2	1	1	0	0
Statistically Significant Asymmetry	Yes	Yes	Yes	No	Yes	Yes

Includes stopped drives as impaired

There were five subjects whose driving tests were prematurely stopped due to somnolence in the two driving studies. Three driving tests were stopped following the 40 mg dose, and two following the 20 mg dose. The SDLP data from all prematurely stopped driving tests were included in the analysis, with the exception of one subject who repeated the treatment period for which her repeat data were used. The absolute SDLP values obtained during the prematurely stopped driving tests were generally consistent with the mean SDLP values in this study, and the individual SDLP differences from placebo did not always exceed the clinical significance bound of 2.4 cm. This lack of relationship between SDLP and prematurely stopped driving is consistent with that reported in literature. All subjects with stopped drives on suvorexant had voluntarily requested that the drive should be stopped, and all self-reported moderate severity AEs of somnolence before or during the drive. This observation is in contrast with driving study experience with other hypnotics where the driving instructor halts the drive more frequently than the driver by a 4:1 ratio.

There was no apparent trend for increased suvorexant plasma concentration in the subjects whose driving was prematurely stopped. Plasma concentrations were obtained one hour after completion of the driving tests in both studies (11 h postdosing), and the PK-PD relationship was explored for SDLP. However, only a very weak correlation between plasma suvorexant concentration and treatment difference on SDLP was observed, and no threshold concentration for SDLP increases >2.4 cm could be identified.

Phase III

To evaluate the potential effects of suvorexant on driving-related safety in the Phase III trials, and in response to feedback from the FDA, occurrences of motor vehicle accidents (MVAs) and moving traffic violations were collected for patients who drove a motor vehicle. At each visit, patients reported the occurrence of any motor vehicle accidents and/or citations which occurred since the last visit and while they were the driver, as well as any related injuries sustained. In total, these assessments were performed on over 1900 patients. The incidence of MVAs and citations was generally similar across the treatment groups in patients treated for up to 3 months (Table 20). Differences in the occurrence of

MVAs and citations in patients treated for extended duration of up to 6 months with suvorexant 15/20 mg and up to 12 months with suvorexant 30/40 mg were also generally comparable between the treatment groups, as shown in Table 21 and Table 22. The incidence of these events across treatment groups were comparable within each age subgroup (non-elderly and elderly), though somewhat lower overall in the elderly.

In addition, accident-related injuries occurring when the patient was the driver were designated as events of clinical interest, requiring prospective assessment and additional data collection. The incidence of accident-related injuries was low and similar across treatment groups: 0.3%, 0.3%, and 0.6% for patients treated with suvorexant 15/20 mg, suvorexant 30/40 mg, and placebo, respectively. Adverse events reported were notably contusions and musculoskeletal injuries; none were associated with somnolence. In all but one case, the patient was the victim of another driver or swerved to avoid an accident.

Table 20. Patients with motor vehicle accidents and/or violations (MVAV) combined Phase III population 0-3 months (P028, P029, P009) (All patients as treated)

	Suvo 15/20mg n (%)	Suvo 30/40mg n (%)	Placebo n (%)
Patients in population with one or more MVAV events	342	569	531
with no MVAV event	10 (2.9)	13 (2.3)	12 (2.3)
	332 (97.1)	556 (97.7)	519 (97.7)
Number of MVAV events	11	14	13
Number of Patients with Accidents	4 (1.2)	7 (1.2)	5 (0.9)
Number of Accidents	4	7	5
Number of Patients with citations [†]	6 (1.8)	7 (1.2)	7 (1.3)
Number of citations [†]	7	7	8
Only patients who were treated and drove during the indicated phase of the study period were included in the table. For Protocol 009, only 12 patients were included in the 0-3 month interval due to a protocol amendment that added the MVAV form; this was implemented after enrollment completed.			
Citation = violation.			
Suvo 15/20mg = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.			
Suvo 30/40mg = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.			

Table 21. Patients with motor vehicle accidents and/or violations (MVAV) combined Phase III population 0-6 months suvorexant 15/20 mg (P028, P029) (All patients as treated)

	Suvo 15/20mg n (%)	Placebo n (%)
Patients in population with one or more MVAV events	342	532
with no MVAV event	12 (3.5)	14 (2.6)
	330 (96.5)	518 (97.4)
Number of MVAV events	13	16
Number of Patients with Accidents	4 (1.2)	7 (1.3)
Number of Accidents	4	7
Number of Patients with citations [†]	8 (2.3)	8 (1.5)
Number of citations [†]	9	9
Only patients who were treated and drove during the indicated phase of the study period were included in the table.		
Citation = violation.		
Suvo 15/20mg = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.		

Table 22. Patients with motor vehicle accidents and/or violations (MVAV) combined Phase III population 0-12 months suvorexant 30/40 mg (P028, P029, P009) (All patients as treated)

	Suvo 30/40mg n (%)	Placebo n (%)
Patients in population	891	692
with one or more MVAV events	36 (4.0)	22 (3.2)
with no MVAV event	855 (96.0)	670 (96.8)
Number of MVAV events	39	27
Number of Patients with Accidents	13 (1.5)	10 (1.4)
Number of Accidents	13	10
Number of Patients with citations [†]	24 (2.7)	14 (2.0)
Number of citations [†]	26	17
Only patients who were treated and drove during the indicated phase of the study period were included in the table.		
† Citation = violation.		
Suvo 30/40mg = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.		

Summary

As described above, the safety profile of suvorexant relative to next-day functioning was studied using multiple tools and different methodologies. For the great majority of patients, suvorexant was not associated with detectable or problematic next-day impairment, as evidenced by performance on cognitive and psychomotor tasks, adverse event reporting, and driving performance. However, as noted above, a small minority of patients did experience some next-day somnolence which was generally mild and self-limited, and an even smaller number experienced more pronounced and/or persistent daytime sleepiness. While the majority of patients taking suvorexant nightly for extended periods had no complaints of residual morning sleepiness or impairment in tasks such as driving, a few individuals did experience somnolence that they felt might impair their ability to drive.

In conclusion, the sponsor has conducted extensive testing on residual effects in suvorexant and believes that these effects are well characterised and are appropriately addressed in the proposed PI.

In the post marketing environment, the sponsor has a robust pharmacovigilance system through which the safety profile of all marketed products is monitored on an ongoing basis. All adverse events received are entered into the company safety database. The company conducts individual report reviews of these events on an ongoing basis. Furthermore, regularly scheduled signalling activities on all marketed products are performed in order to ensure that the safety profile of all products is current and consistent with the most recent available data.

In addition to this, the sponsor proposes to implement an event specific questionnaire for the purpose of supplementing standard post approval surveillance for motor vehicle accidents. This will allow further characterization of these events.

OPR evaluator's comment

The OPR evaluator does not consider the submitted study results and conclusions drawn from them sufficient to indicate that the residual effects of suvorexant are sufficiently characterised to allow patients to operate machinery or drive vehicle the next day.

The studies presented seem to have the following issues:

- The study size is too small. In order to obtain more meaningful results, a larger study size should be used to narrow the confidence intervals.
- 90% confidence intervals have been used. This is unusual, as most driving studies that evaluate the effect on driving using Δ SDL (change in standard deviation of lateral position) use a 95% confidence interval. As an example, had a 95% confidence interval

been used, it may have been likely that the graph in Figure 2 would have shown a confidence interval upper limit for suvorexant 40 mg beyond the cut-off value of 2.4 cm, indicating impairment at this dose, at least for some people in this group, or at the very least indicating inconclusive results.

- The average values are not always representative. For a small number of individuals, the Δ SDL_P value may have been significantly higher.
- The Δ SDL_P cut-off of 2.4 cm is commonly used to assess driving ability, as it is regarded as an equivalent of a BAC (blood alcohol concentration) of 0.5 g/L, which is the legal limit in many countries. But even lower Δ SDL_P values are considered to be associated with moderate impairment, for example, a Δ SDL_P value of 1.94 cm for zopiclone^{14,15}. It is established that zopiclone impairs driving ability. In the data presented by the sponsor using their 90% CI (Figure 2), the Day 9 Δ SDL_P values and associated CIs for zopiclone 7.5 mg and suvorexant 40 mg are very similar.
- Middle of night dosing has not been tested. A new study should incorporate results for 4 to 6 hours after middle of the night dosing, 10-11 hours after bed time dosing, and 16 to 17 hours after bed time dosing.
- Given that 10 mg seems to be a more appropriate dose to use, this dose should be tested.
- The presented studies have not included a correlation with suvorexant plasma concentration. Given the long onset time and the long half-life of this first in class medicine, a correlation with 4 to 6 hours after middle of the night dosing, 10 to 11 hours after bed time dosing, and 16 to 17 hours after bed time dosing, would be essential.

Suvorexant is a first in class, new chemical entity, which has not been used outside a controlled environment. Given the lack of postmarket experience, and given the incomplete data available on residual effects, the recommendation remains. The sponsor should conduct additional pharmacovigilance activities to address residual effects further, particularly effects on driving and operating machinery. Until such activities have sufficiently proven that suvorexant is safe to use with regard to residual effects, the PI should state that patients treated with suvorexant should not drive or operate machinery the day after administration, in particular those on a higher dose, the elderly, and those on concomitant CNS medications (or a statement to that effect). This statement can be reviewed once sufficient favourable data is available.¹⁶

Recommendation 5 in RMP evaluation report

In order to assess off-label use, the sponsor should either conduct a drug utilisation study, or make the results of such a study available to the TGA.

Sponsor's response (or summary of the response)

The sponsor is currently evaluating the feasibility of conducting a drug utilization study in Australia. However, the sponsor notes that the origin of the question relates to the proposed change in indication made by the clinical evaluator. The response below was received from the TGA following a request for clarification of comment 6:

¹⁴ Leufkens TR, Vermeeren A 2009. Highway driving in the elderly the morning after bedtime use of hypnotics: a comparison between temazepam 20 mg, zopiclone 7.5 mg, and placebo. *J Clin Psychopharmacol* 29(5):432-8

¹⁵ Leufkens TR, Vermeeren A 2014. Zopiclone's Residual Effects on Actual Driving Performance in a Standardized Test: A Pooled Analysis of Age and Sex Effects in 4 Placebo-Controlled Studies. *Clin Ther* 36(1):141-50.

¹⁶ See also *Sponsor response* on page 90-91.

'Given that the clinical evaluator supports an indication different to the indication proposed by the sponsor, an indication restriction is a possibility. To accommodate this, the recommendation in question was made. The issue has also been referred to ACSOM for advice.'

In relation to the suggested restriction to the duration of use, the sponsor would like to point out that the dossier included a safety study conducted with the higher doses (PD009) for a 12 month duration. Therefore, data has been presented for use after 3 months.

Similarly, the proposed restriction to primary insomnia is based on DSM-IV, and due to evolving thinking in the sleep field about the most correct terminology for insomnia, the DSM-V no longer distinguishes primary from secondary insomnia (see response to TGA comment 8).

Furthermore, to date the sponsor has not been able to identify an Australian database that would allow the evaluation of drug utilization in private pay patients. The sponsor anticipates that a substantial proportion of the usage of suvorexant will be private pay.

However, the sponsor would welcome further advice from the TGA regarding these matters.'

OPR evaluator's comment

In response to the concern raised by the sponsor with regard to private pay, the clinical evaluator has suggested general practice patient management systems to enable linking prescription, indication and duration of use.

Recommendation 6 in RMP evaluation report

In order to assess drug misuse and diversion the sponsor should either conduct a post authorisation surveillance study, or make the results of such a study available to the TGA.

Sponsor's response (or summary of the response)

'After approval in the US, Merck plans to monitor the US Drug Abuse Warning Network (DAWN) and will report in the Periodic Safety Update Report (PSUR) the number of DAWN events with use of suvorexant. Monitoring in the US will be more effective and faster than in Australia because of the larger US population size and larger projected sales in the US. The Drug Abuse Warning Network (DAWN) is a US public health surveillance system that reports on drug-related visits to non-Federal, short-stay general medical and surgical hospital emergency departments (EDs). DAWN collects data on illegal drugs, prescription and over-the-counter medications, dietary supplements, inhalants and alcohol. DAWN is used to monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug use and abuse, and estimate the impact of drug use, misuse, and abuse.'

OPR evaluator's comment

A post authorisation surveillance study in the US may be considered acceptable, but it appears that suvorexant has not been approved for use in the US.¹⁷

As a result, the sponsor should conduct a local post authorisation surveillance study to assess drug misuse and diversion.

Recommendation 7 in RMP evaluation report

The indication should be restricted to use in primary insomnia up to three months only, that is, no use in secondary insomnia, and no long-term use.

¹⁷ Subsequent to this report, suvorexant was approved by the US FDA and the Japan HMLW. See Table 1.

Sponsor's response (or summary of the response)

The sponsor will evaluate the above comment pertaining to the indication in the context of the Delegate's Overview when available. The sponsor provides perspective below regarding the indication for consideration.

Due to evolving thinking in the sleep field about the most correct terminology for insomnia, the DSM-V no longer distinguishes primary from secondary insomnia. This change in the DSM-IV is in practical recognition that insomnia most commonly co-exists with other conditions, and that these may have reciprocal influence on symptoms.

Conditions associated with insomnia are best described as being 'comorbid' (rather than designating that insomnia in these instances is secondary), to emphasize that treatment targeting each condition separately is often warranted. Disturbed sleep has been shown to increase anxiety and pain severity, and insomnia co-therapy can improve sleep and outcome of the comorbid condition (for example major depressive disorder (MDD), Generalised anxiety disorder (GAD), and rheumatoid arthritis) – arguing for concurrent treatment of insomnia in patients with other conditions.

The Phase II/III studies of suvorexant endeavoured to enrol patients with primary insomnia, according to the DSM-IV criteria of the time, to strive for evaluation of suvorexant efficacy and safety in the least potentially confounded population possible, in full recognition of the reality that insomnia in isolation is rare. The sponsor feels that through this approach the efficacy and safety of suvorexant has been comprehensively assessed and demonstrated in these patients, despite the presence of a variety of concurrent conditions that more accurately reflect practical use in clinical practice. The medical histories of patients in the Phase II/III program are provided in the CSRs for the individual trials.

On the basis of the comprehensive Phase II/III assessment in insomnia patients, and to ensure that suvorexant product labelling in Australia reflects the latest in sleep expert opinion about the appropriate terminology for *the condition of insomnia, the sponsor suggests that the term "insomnia" be used instead of "primary insomnia"*.

The sponsor also provides additional information regarding the long-term efficacy of suvorexant beyond 3 months, for consideration. A post hoc analysis of the 3 month Extension Phase of Protocol 028 based on the Full Analysis Set (FAS) for the pooled 028 and 029 study data, is provided as part of the sponsor's response to the *Additional questions from the Delegate (Comment 1)* above pertaining to request for additional pooled efficacy data. The results of this analysis provide evidence which supports the long-term sleep maintenance and onset efficacy of suvorexant HD for up to 6 months and of suvorexant LD for up to 5 months.

Furthermore, a 1 year placebo-controlled long-term safety trial (P009) provides additional evidence for the ability of suvorexant 30/40 mg to provide sustained improvements in sleep onset and sleep maintenance in the setting of chronic insomnia. The P009 study results indicate that insomnia patients continue to benefit from suvorexant 30/40 mg treatment (beyond a year), and that insomnia symptoms return, with no rebound, in patients upon cessation of suvorexant treatment. Please refer to the response to the Additional questions from the Delegate (Comment 1) and also to P009 CSR.

OPR evaluator's comment

The OPR evaluator acknowledges the recent change to the DSM-V. However, the DSM remains only one of the many disease classification systems. Other important classification systems relevant to sleep disorders include the International Classification of Sleep Disorders (2nd edition) (ICSD-2), or the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian Modification (ICD-10-AM). It is

noted that neither of these classification systems have discarded the term 'primary insomnia', even though this may eventuate in the future.

The OPR evaluator has no objection to align the indication to reflect current terminology. However, the approved indication needs to reflect the conditions in which the drug has been shown to be effective. Furthermore, a change in classification in the DSM may not necessarily congruent with common usage of terms related to insomnia. The term 'primary insomnia' is likely to be used for a long period of time. The change in terminology needs to be generally accepted and understood, that is, genuinely become current terminology, before an adaptation should be attempted. A change in indication due to changes in terminology must not lead to an unapproved perceived extension of indication that may lead to inadvertent off-label use.

With regard to restricting use to 3 months, the OPR evaluator supports the clinical evaluator.

Recommendation 8 and 9 in RMP evaluation report

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised and that the draft consumer medicine information document be revised to accommodate the changes made to the product information document but the scope of the proposed revisions are beyond the scope of this AusPAR.

Summary of recommendations

Outstanding issues

It is considered that the sponsor's response to the TGA's request for further information has not adequately addressed all of the issues identified in the RMP evaluation report. Additional recommendations are made.

Additional recommendations

See Points 3-5 below.

Summary of outstanding issues (incorporating the additional recommendations made in this report)

Recommendations in regard to pharmacovigilance activities

1. The sponsor should consider conducting additional pharmacovigilance activities to address residual effects further, particularly effects on driving and operating machinery.
2. In order to assess drug misuse and diversion the sponsor should conduct a post authorisation surveillance study in Australia.
3. Appropriate additional pharmacovigilance activities should be conducted to investigate the potential use of suvorexant as a depressant ('downer') or existing appropriate additional risk minimisation activities should be assigned.
4. Appropriate additional pharmacovigilance activities should be conducted to investigate the use in polypharmacy to evaluate the effect of interactions, such as falls in the elderly, or existing appropriate additional risk minimisation activities should be assigned.
5. Appropriate additional pharmacovigilance activities should be conducted to investigate safe concomitant psychiatric drug use (other than paroxetine), or existing appropriate additional risk minimisation activities should be assigned.

Recommendations in regard to risk minimisation activities

1. The indication should be restricted to use in primary insomnia up to three months only, that is, no use in secondary insomnia, and no long-term use.
2. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:
 - a. In the 'Precautions' section, the PI should include a statement that suvorexant should not be used in children rather than that it is not recommended in children (or a statement to that effect).
 - b. In the 'Precautions' section, the PI should include a statement PI should state that patients treated with suvorexant should not drive or operate machinery the day after administration, in particular those on a higher dose, the elderly, and those on concomitant CNS medications (or a statement to that effect).
 - c. In the 'Precautions' section, the PI should include a statement that the lowest dose possible that addresses insomnia should be used to minimise adverse events (or a statement to that effect).
 - d. In the 'Interactions with other medicines' section, the PI should include a numerical value for increased suvorexant exposure during concomitant administration with ketoconazole and diltiazem respectively (or a statement to that effect).
 - e. In the 'Adverse Events' section, the PI should include dysgeusia, urinary tract infection, sleep paralysis, hallucination as adverse events.
 - f. In the 'Dosage and Administration' section, the PI should include a titration schedule in the proposed PI for separate patient groups with different dosing needs (including elderly patients, female patients, or obese patients).
 - g. In the 'Dosage and Administration' section, the PI should reflect any dosing recommendations made (or a statement to that effect).
3. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM) (Summary)

General

- The properties of suvorexant and orexin receptors are not fully characterised.
- Suvorexant has the potential for widespread use.

Pharmacology

- Peak concentration is at approximately 3 hours, with a long, dose-dependent half-life.
- As bioavailability falls with increasing doses, a dose of 10 mg is as efficient as a dose of 40 mg, making it less suitable to treat insomnia.
- Interactions with CYP3A inhibitors or CYP3A inducers can result in up to a 3 fold increase or 8 fold decrease in concentration respectively.
- Safe concomitant psychiatric drug use, except with paroxetine, has not been established.
- The most favourable benefit/risk profile was seen with the 10 mg dose; there seems to be no benefit of upward titration.

Ongoing safety concerns

- The safety concerns associated with suvorexant are significant both in terms of effects on the individual user and also the potential effects on others. A situation where its use would be safe, such as taking the medication at 6pm, not driving the next day and not having any other co-morbidity, the committee was very concerned that this was unrealistic. Users should not self-assess their ability to drive.
- There are significant levels of sedation up to 16 hours after dosing, that is, impaired driving ability for this period. Results from driving studies suggest impaired driving performance as an effect of suvorexant, with the risk underestimated for overweight and female patients who are likely users.
- Other potential serious risks associated with suvorexant use include suicidal ideation, impaired balance which might lead to increased risk of falls, sleep paralysis, effects of overdose, use in different population groups, including patients with mood disorders or those who were prone to substance abuse.

Proposed pharmacovigilance and risk minimisation activities

- The committee advised that the proposed pharmacovigilance and risk minimisation activities were not sufficient.
- Additional data is required on the safety of the drug in a real-world situation.
- A drug utilisation study would be important to evaluate off-label use, abuse, misuse and diversion, including the potential use as a 'downer', use in polypharmacy to evaluate the effect of interactions, such as falls in the elderly.

Suggested wording for conditions of registration

RMP

Implement EU-RMP Version 1.0 (dated 29 January 2013, Data Lock Point (DLP) 29 November 2012) and Australian Specific Annex (dated 21 February 2013, DLP not given), and any future updates (where TGA approved) as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections in respect of Chemistry, Manufacturing, Controls and Biopharmaceutics to registration of these products.

Suvorexant has one chiral centre. Two enantiotropically related anhydrous polymorphs have been identified; Forms I and II. Although Form I is more stable at 25°C, Form II was chosen for commercial development as it is easier to process.

A less than dose proportional increase in exposure over the dose range is evident, driven largely by the exposures observed at the 30 mg IV dose which were lower than expected based on 5 mg to 20 mg IV dose exposures in humans. The company claimed that this may be influenced by inter-panel differences due to the limitations of conducting the study as a parallel design. The observed results from the supplemental assessment of dose proportionality suggest that exposures over the 5 mg to 20 mg dose range more closely approximate dose-proportionality as compared to the 5 mg to 30 mg dose range. In

addition, exposures in the 5 mg to 20 mg IV dose range approximated those of the 15 mg to 40 mg oral dose range investigated in the Phase III studies.

Nonclinical

There are no nonclinical objections to the registration of suvorexant.

The pharmacological studies afforded nonclinical support for the proposed mechanism of action and therapeutic effect of suvorexant.

In general, the toxicological profile of suvorexant was unremarkable. The main findings were reasonably attributed to hepatic enzyme induction, particularly in rats, leading to hepatocellular and thyroid hypertrophic responses. This mechanism is well-recognised and not considered significant for human risk assessment.

Suvorexant crossed the placenta in rats and rabbits, and was excreted in rat milk. There was no evidence of teratogenicity in rats and rabbits treated orally with suvorexant during organogenesis, with suvorexant exposures (AUC) approximately 50 times clinical exposure (M9 exposure 2 times in rats and >30 times in rabbits).

An increased incidence of mild retinal atrophy was observed in the rat carcinogenicity study at plasma AUC exposures \geq 7 times clinical AUC (NOEL 4 times clinical). This may represent exacerbation of an age-related change in this species.

There was some evidence for cataplexy following food enrichment in dogs, with suvorexant and also other orexin receptor antagonists but this was not confirmed in a monkey oral study. The clinical relevance of these effects is not known.

The minor (S) enantiomer impurity in the drug substance has been only partly qualified at the sought specification.

Clinical

The clinical evaluator considered the benefit-risk balance of suvorexant to be unfavourable given the proposed usage but would become favourable if the dosing recommendations were amended as described in his report. The major amendments are a) that the type of insomnia be restricted to primary insomnia and b) that the duration of use should not exceed 3 months.

The following revised indication was recommended:

Rivuley/Silumbra/Vispli/Belsomra is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Pharmacokinetics

The absolute bioavailability of suvorexant reduces with increased dose of drug. From population PK modelling the mean (5th and 95th percentile) estimated bioavailability was 82% (0.74 to 0.89) for a 10 mg oral dose, 62% (0.55 to 0.69) for a 20 mg dose, 47% (0.41 to 0.53) for a 40 mg dose and 37% (0.31 to 0.42) for an 80 mg dose. Thus between the 10 mg and 20 mg doses a doubling of dose results in a ~50 %increase in the amount of available suvorexant.

The different tablet strengths are bioequivalent with single doses of 2 x 15 mg tablets bioequivalent to a 30 mg tablet and 2 x 20 mg tablets bioequivalent to a 40 mg tablet. There was no significant difference in the AUC for suvorexant taken with food compared with taken fasted however the C_{max} was increase by 9% and 23% in Studies P020 and P042 respectively and the T_{max} increased by about 1.5 hours.

Geometric mean T_{max} was 2 hours when given fasted and 3 hours when given with a high fat meal (Study P020). The mean apparent terminal half-life was around 10.6 hours fasted and 11.6 hours fed. V_{ss} ranged from 36.5 L to 57.33 L. Steady state was reached in about 3 days. The accumulation ratio was 1.3 to 1.5 for both AUC and C_{max} at the proposed doses. Suvorexant is highly protein bound (approximately 99%) in subjects with normal hepatic function.

Suvorexant undergoes extensive hepatic metabolism involving CYP3A4, CYP2C19 and glucuronidation. Clearance (CL) ranged from 48.60 to 80.62 mL/min and apparent terminal half-life from 8.9 hours to 13.5 hours. The primary metabolites are: M4 (21.1% of dose), M18 (10.6%), M9 (9.5%) and M10a (9.2%). None of the metabolites appear to be active. The metabolites are excreted in bile (around 80% of the recovered dose of radioactivity in a mass balance study) and renally (around 20% of recovered dose of radioactivity).

Moderate impairment of hepatic function (Child-Pugh score 7 to 9) did not significantly alter the metabolism of suvorexant. Severe renal impairment was associated with a mean 22% increase in the AUC and a 15% increase in the C_{max} of suvorexant.

Men aged over 65 years had a mean 28% reduction in C_{max} compared with young men but the AUC was similar. The mean apparent half-life of 12 hours observed in elderly men was slightly longer than that seen in young male subjects. In women aged over 65 years the mean AUC was 55% higher and the AUC for the M9 metabolite was increased by a mean of 30% compared to elderly men.

Ketoconazole, a potent inhibitor of CYP3A4 was associated with a 279% increase in AUC and a 23% increase in the C_{max} of suvorexant; and the AUC for M9 increased by 80% and the C_{max} of M9 decreased by 39%. Co-administration of diltiazem (a substrate and moderate inhibitor of 3A4) was associated with an approximate doubling of the AUC for suvorexant. Rifampicin (a potent inducer of multiple CYP enzymes) greatly decreased the AUC of suvorexant. Oral contraceptives (ethinyl oestradiol and norelgestromin), paroxetine (an inhibitor of CYP2D6) and ethanol did not significantly affect the metabolism of suvorexant.

Suvorexant appears to be an inhibitor of CYP3A4. The PK of a single dose of suvorexant did not alter the AUC for midazolam but at steady state suvorexant was associated with a 47% increase in the AUC of midazolam. The AUC of digoxin was increased by a mean of 27% when given with suvorexant. Suvorexant did not affect the PK of warfarin or ethanol.

Pharmacodynamics

Sleep is characterised by two distinct stages: REM sleep (rapid eye movement, paradoxical or "dream" sleep) and non-REM (NREM or non-rapid eye movement) sleep (75 to 80% of sleep in healthy adults). NREM sleep is further divided into: Stage 1 sleep (2 to 5%), which occurs at the awake-sleep transition; Stage 2 sleep (45 to 55%), which is considered the beginning of 'true' sleep and is characterised by sleep spindles and high amplitude K-complexes; Stage 3 and Stage 4 sleep (3 to 23%), also known as "deep sleep," slow wave sleep or delta sleep, during which the highest threshold to sensory arousal occurs. REM sleep is characterised by atonia or nearly absent skeletal muscle tone (except for extra-ocular muscles and respiratory muscles), significant cortical activity ('paradoxical sleep') that is associated with dreaming, irregular respiratory and heart rates and episodic bursts of phasic eye movements. NREM and REM sleep alternate throughout the night in cycles of approximately 90 minutes and are occasionally interrupted by transient micro-arousal states followed by rapid return to deeper stages of sleep.

The effect of suvorexant on sleep architecture was examined in Study P002, a randomised, double-blind, placebo-controlled 5-period, crossover study to evaluate the effects of single doses of suvorexant (10 mg, 50 mg and 100 mg) on polysomnogram (PSG) in healthy male

subjects. A single oral dose of suvorexant or placebo was administered in each treatment period (periods 1 to 5). Study treatments were given 1 h before each subject's habitual sleep time. There was a minimum of 96 hours washout prior to the beginning of the next treatment period. In Period 5 no PSG recording was obtained, only blood samples for PK assessments were collected. Blood samples for PK assessment were also collected on nights PSG recording were made.

The primary endpoint in this study was slow wave activity (SWA) in the first half of the night (μ V²/Hz; micro-voltage squared per Hertz (Hz)), which was defined as the power spectral density of delta frequency band in the first 4 h of the 8 h PSG recording. The secondary endpoint was REM sleep duration (min) during the second half of the night (REM2) which was defined by the duration of REM Stage during the second 4 h during the 8 h PSG recording.

Additional exploratory pharmacodynamic endpoints in Study P002 included psychomotor performance tests such as by Simple Reaction Time (SRT), Choice Reaction Time (CRT), and Digit Symbol Substitution Test (DSST). The effects of suvorexant on psychomotor performance were evaluated at 10 h post dose.

In this group of healthy young men there was little effect on slow wave activity, even with doses of 100 mg. The geometric mean duration of REM2 increased in a dose dependent manner and was 7.35 minutes longer in the second sleep period with 100 mg suvorexant than with placebo. Confidence intervals for the difference overlapped. Sleep latency decreased in a dose dependent manner, from a geometric mean of 12.60 minutes for placebo to 2.88 minutes for 100 mg suvorexant. Wake after sleep onset (WASO) improved with suvorexant but not in a dose dependent manner. Sleep efficiency increased in a dose dependent manner up to 100 mg but the absolute difference was small at around 4 minutes. Psychomotor performance tests including Choice Reaction Time (CRT), Digit Symbol Substitution Test (DSST) and Simple Reaction Time (SRT) all deteriorated in a dose dependent manner.

Studies P003 (10 to 100 mg suvorexant), P011 (150 to 240 mg suvorexant) and P005 (to 76 mg suvorexant) were primarily PK studies but some data on psychomotor effects were obtained. There was a consistent pattern of reduced alertness associated with healthy subjects taking suvorexant in those studies. This contrasts with Studies P032, P036, P035 and P039 (N= 103) where the effects of suvorexant on next-day memory and balance were evaluated using word learning test (IDWR) and body sway test (AccuswayTM), respectively, following night time administration of suvorexant. No significant effects were seen in P032, P036 or P039 however in non-elderly subjects (P035; high-way driving study in non-elderly subjects), there was a statistically significant decrease in word recall after the words were presented to subjects in the morning 11 hours after a single dose of 40 mg suvorexant; and there was a statistically significant increase on body sway area in the morning 11 hours following single dose of 20 or 40 mg suvorexant.

The next-day effects of suvorexant on psychomotor performance were evaluated using a digit symbol substitution test (DSST), simple reaction time (SRT) and choice reaction time (CRT) in five clinical pharmacology studies (P002, P035, P039, P032, P036) following evening administration (9 to 11 h postdose) of suvorexant in 125 subjects. DSST was evaluated in all five studies. Four studies did not show significant treatment effects on DSST (# of correct) with suvorexant compared to placebo. However, in one (P035; non-elderly driving study), there was a statistically significant decrease in number of correct for DSST (3 item decrease) at approximately 11 h following a single dose of 40 mg suvorexant compared to placebo. There were no effects on DSST following 8 day consecutive doses of suvorexant in this same study (sponsor's *Summary of clinical safety*).

Effects of suvorexant on the ability to drive were examined in Studies P035 and P039. P035 was a randomised, double-blind, placebo and active controlled, multiple dose, 4-

period crossover study to evaluate highway driving performance following evening administration of suvorexant, zopiclone (active control), and placebo in healthy non-elderly adults. There were 28 or 27 subjects in each of the 4 study groups. Subjects received 2 dose levels of suvorexant (20 mg and 40 mg) or placebo consecutively for 8 days in each treatment period. Zopiclone 7.5 mg was used as an active control to demonstrate assay sensitivity since it has consistently demonstrated moderate next-day impairment on driving performance in previous highway driving studies.

Driving performance was assessed on Day 2 and Day 9 approximately 9 h post dose in each treatment period. The standardized highway driving test is a functional measurement to predict traffic safety. The FDA recommended the next-day residual effects of suvorexant be evaluated via driving performance. The highway driving test employed in this study has been standardised and used to evaluate drugs' effect on driving performance including alcohol, benzodiazepines, zopiclone, zolpidem and zaleplon.

The primary endpoint in this study was the standard deviation of lateral position (SDLP in centimetres) from the highway driving test. In the standardised highway driving test, subjects operated a specially instrumented vehicle over a 100 km primary highway circuit to maintain a constant speed of 95 km/h and a steady lateral position between the delineated boundaries of the slower traffic lane. SDLP was calculated as the square root of the pooled lateral position variance. SDLP is an integrated measure of road tracking error or "weaving". Zopiclone had consistently shown an increase on SDLP (approximately 2.5 cm) in the highway driving tests at 10 h postdose comparable to those found for alcohol when blood alcohol concentration is 0.5 g/L or more.

Alcohol at a blood concentration of 0.5 g/L, which is the legal limit for driving in many countries including Australia, produced a mean increase on SDLP of approximately 2.4 cm. If the 90% confidence interval for the observed mean treatment difference between suvorexant and placebo on SDLP lay below 2.4 cm, the treatment effect was to be considered not considered clinically meaningful.

In addition to the analysis around mean SDLP, a symmetry analysis with the SDLP data was also conducted. Symmetry analysis is a statistical method to determine whether the distribution of changes on SDLP (treatment versus placebo) above and below certain threshold values is symmetric around zero. This analysis evaluated whether there was a difference between the number of subjects who have increases on SDLP (treatment versus placebo) compared to the number of subjects who have a decrease on SDLP (treatment versus placebo). Results of the symmetry analysis are in Table 23. The 20 mg and 40 mg doses of suvorexant had less effect on mean SDLP than did the recommended 7.5 mg dose of zopiclone and the 40 mg dose had more effect than the 20 mg dose. The studies criteria for no clinically meaningful effect were met. However 6/27 (22%) of individuals given the 20 mg suvorexant dose had SDLP \geq 2.4 cm on Day 2, consistent with the SDLP in individuals with a blood alcohol reading of 0.5 g/L. Some 14/28 (50%) of subjects given zopiclone also had SDLP \geq 2.4 cm on Day 2.

Table 23. Study P035: Results of Symmetry Analysis for Individual SDLP Differences (Active - Placebo) at Cut Point of 2.4 cm Following PM Administration of Suvorexant (MK-4305) 20 mg, 40 mg Single Dose (Day 2) and Multiple Doses (Day 9), and Single Dose of Zopiclone 7.5 mg (Day 2 and Day 9) (N=28 on Day 2, N=27 on Day 9)

Treatment	Day=2			Day=9		
	Suvorexant 20 mg	Suvorexant 40 mg	Zopiclone 7.5 mg	Suvorexant 20 mg	Suvorexant 40 mg	Zopiclone 7.5 mg
n+1 [†]	6	10	14	2	6	8
n-1 [‡]	0	2	1	1	0	0
m = n+1 + n-1	6	12	15	3	6	8
Test Statistic [§]	2.45	2.31	3.36	0.58	2.45	2.83
Reject Null Hypothesis?	Yes	Yes	Yes	No	Yes	Yes

[†]n+1 = number of subjects with treatment difference (from placebo) \geq 2.4 cm.
[‡]n-1 = number of subjects with treatment difference (from placebo) \leq -2.4 cm.
[§]Test Statistic = $(n+1 - n-1)/\sqrt{m}$.
^{||}Reject Null hypothesis if test statistic > 1.74 , which is the critical value for general sign test with exact unconditional approach for sample size N=28 and N=27.
Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.
Original Period 2, Day 2 data for AN0016 was not included in the analysis (the subject had a premature stop due to somnolence). The subject could not return for the Period 2, Day 8 visit and repeated this period. Only the repeat period is included in the analysis.

Study P039 was similar to Study 035 but assessed subjects aged over 65 years given 15 mg and 30 mg suvorexant. Less effect on driving ability was seen in this study than in Study P035. Suvorexant was not associated with prolongation of the QT interval.

The abuse potential of suvorexant was assessed in Study P025, a randomised, double blind, balanced, placebo and active controlled, six-way crossover study of the abuse potential of suvorexant in 36 healthy recreational drug-users. In that study suvorexant (40 to 150 mg) likeability was not statistically different from that of zolpidem 15 mg or 30 mg. There was a trend towards preference for zolpidem. The adverse events database was also interrogated for pre-specified events that were potentially associated with abuse. These included: depersonalization; derealisation; dissociation; euphoric mood; hallucination; mania; and potential study medication misuse. Across the Phase III study population during the first 3 months of study treatment the incidence of these events (pooled) was 2% for suvorexant HD, 3.2% for suvorexant LD and 2.2% for placebo.

Suvorexant did not impair respiratory safety during sleep at doses up to 150 mg in healthy volunteers. In Study P040 there was no impairment of mean oxygen saturation (SaO_2) during total sleep time, during wake time, non REM or REM. There was no impairment of the apnoea-hypopnoea index. Suvorexant and alcohol exhibited a significant additive effect on impairment in cognitive function that lasted for up to 9 hours post-ingestion. For digit reaction time, targets detected correctly, words correctly recalled, numeric working memory sensitivity index and alertness there was significant additive impairment. The effect of suvorexant in subjects with chronic obstructive pulmonary disease (COPD) was examined in Study P032. There were 24 subjects in this study and a small proportion (0.2%) of time with PO_2 saturation below 85% was seen when subjects were given HD suvorexant compared to placebo. There were small differences for mean O_2 saturation during the various sleep phases.

The effect of suvorexant in subjects with mild to moderate obstructive sleep apnoea was examined in Study 036. This was a double-blind, placebo-controlled, 2-period, crossover study in which 26 subjects with mild to moderate obstructive sleep apnoea received 40 mg suvorexant or placebo for 4 consecutive days. Severity of obstructive sleep apnoea was assessed using the Apnoea-hypopnoea Index (AHI). The AHI combines panes and hypopneas. The apnoea must last for at least 10 seconds and are associated with a decrease in blood oxygenation. Combining these gives an overall sleep apnoea severity score that evaluates both number sleep disruptions and degree of oxygen desaturation. The AHI is calculated by dividing the number of events by the number of hours of sleep. Major exclusion criteria were: severe sleep apnoea (AHI $>30/\text{hour}$), use of continuous

positive airway pressure (CPAP)¹⁸ and were morbidly obesity. There was a small increase in mean AHI following multiple doses of suvorexant, the observed mean AHI treatment difference (suvorexant – placebo) and 90% confidence interval on Day 4 are 2.66 and (0.22, 5.09).

Multiple doses of suvorexant do not produce a clinically or statistically significant reduction of mean SaO_2 during total sleep time in these subjects however there was a trend towards lower O_2 saturation with suvorexant. The % time O_2 saturation was <90% was 2.16 compared with 1.96 for placebo (difference 0.21 with 90%CI:-0.59, 1.01). The % time O_2 saturation was <85% was 0.69 compared with 0.41 for placebo (difference 0.28 with 90% CI:-0.09, 0.65).

Efficacy

A dose-finding study, two pivotal studies assessing safety and efficacy to 3 and 6 months respectively and a 12 month safety and efficacy study were submitted. Study P006, the dose-finding study is described in the CER. This was a multicentre, randomised, double blind, placebo controlled, two period adaptive polysomnography study to evaluate the safety and efficacy of suvorexant in subjects with primary insomnia. Eligible patients were randomised to one of the 4 suvorexant doses (10, 20, 40, or 80 mg) and to suvorexant/placebo or placebo/suvorexant. The duration of each treatment was for 4 weeks. Sleep efficiency (SE), the primary efficacy endpoint for this study was derived from PSG and is defined as total sleep time (TST) expressed as a percentage of time in bed.

In this study all doses of suvorexant (10 mg, 20 mg, 40 mg and 80 mg) were statistically significantly superior to placebo in improving insomnia as measured by the primary efficacy endpoint of SE, at Night 1 and Week 4. On Night 1 there was a positive dose-response relationship for SE but a dose-response was not demonstrated at the Week 4 assessment. Total sleep time was an exploratory analysis. Total sleep time increased with dose on both Night 1 and Week 4. The estimated differences in TST between Night 1 and baseline were: 52.4, 85.3, 83.7, 113.8 and 104.5 minutes for placebo, suvorexant 10 mg, 20 mg, 40 mg and 80 mg, respectively; and on Week 4 were 59.2, 89.8, 91.8, 97.9 and 95.1 minutes respectively.

The pivotal studies, P028 and P029 are described in the CER. These studies had similar designs, the major difference between them was that P028 included an optional 3 month extension phase after the initial 3 month evaluation phase whereas P029 did not. They were multicentre, randomised, parallel group, studies in adult subjects with a formal diagnosis of primary insomnia using DSM-IV-TR criteria. Major inclusion criteria were:

- Total sleep time of <6.5 hours on at least 3 out of 7 nights each week.
- Sleep latency of ≥ 30 minutes on at least 3 out of 7 nights each week.
- ≥ 1 h of wakefulness after sleep onset on at least 3 out of 7 nights.
- For subjects chronically using a hypnotic or anxiolytic for treatment of insomnia (defined as use of 4 times/week), a 4-week washout (or 5 $t_{1/2}$ lives, whichever is greater) is required.
- Spends 6.5 to 9 hours nightly in bed on at least 3 out of 7 nights each week during the 4 weeks.

The subjects were randomised in two cohorts: Questionnaire only and polysomnogram plus Questionnaire. Subjects were randomised 3:2:3 to high dose (40 mg or 30 mg), low

¹⁸ CPAP, or continuous positive airway pressure, is a treatment that uses mild air pressure to keep the airways open. CPAP typically is used by people who have breathing problems, such as sleep apnea.

dose (20 mg or 15 mg) or placebo.¹⁹ Over 40% of subjects in both studies were aged over 65 years. For subjects randomised to the polysomnogram additional inclusion criteria applied:

- Willing to stay overnight at a sleep laboratory for PSG testing visits
- Willing to stay in bed for at least 8 hours each night while at the sleep laboratory
- Willing to refrain from drinking alcohol on all PSG visit days, and at least 24 hours prior to a PSG visit
- Willing to avoid caffeine after 1 PM (13:00) on PSG visit days
- At baseline: LPS > 20 minutes on both Screening and Baseline PSG nights and a mean WASO of ≥ 60 minutes on the combined Screening and Baseline PSG nights, where neither night can be ≤ 45 minutes.

Subjects were stratified by dose with subjects aged <65 years randomised to receive 40 mg (high dose) or 20 mg (low dose) suvorexant or placebo and subjects aged ≥ 65 years 30 mg (high dose) or 15 mg (low dose) suvorexant or placebo. A total of 1022 subjects received treatment in P028 and 1021 in P029. Of these 75.8% of subjects in P028 and 71% in P029 received polysomnograms. Polysomnograms were performed at screening, baseline and on 3 occasions during the 3 month randomisation period (at Night 1, end of Month 1 and end of Month 3).

The primary efficacy outcomes measures were intended to support the proposed indication for the highest initially proposed suvorexant dose only. They included assessments of sleep maintenance and sleep onset using both the questionnaire (to assess subjective changes) and changes as measured assessed by polysomnogram.

The primary efficacy outcome measures were:

- Sleep maintenance:
 - Suvorexant (high dose): Change from baseline in subjective Total Sleep Time (sTST) on the daily e-diary at Month 1 and Month 3
 - Suvorexant (high dose): Change from baseline in wakefulness after persistent sleep onset (WASO) by PSG at Month 1 and Month 3
- Sleep Onset:
 - Suvorexant (high dose): Change from baseline in mean subjective Time to Sleep Onset (sTSO_m) by daily e-diary at Month 1 and Month 3
 - Suvorexant (high dose): Change from baseline in Latency to onset of Persistent Sleep (LPS) by PSG at Month 1 and Month 3.

Secondary efficacy outcomes were determined for both high and low dose suvorexant regimens. These measures were the same as for the primary criteria but the period of assessment was from baseline to Week 1 for subjective total sleep time and waking after sleep onset and time to persistent sleep. Polysomnogram assessments of total sleep time and waking after sleep onset were compared only from baseline to Night 1. Remaining outcomes measures were exploratory only.

A pooled analysis of results from the pivotal studies P028 and P029 and the dose ranging Study P006 (first period only) was performed in order to develop exposure/response models for the objective and subjective efficacy criteria and for DSST (digit symbol substitution test; a safety parameter) is discussed in the CER. The mean effect of each

¹⁹ In protocol P028. In protocol 029, subjects were randomised 1:1:1 for Q cohort and 2:1:2 for PQ cohort for HD:LD:PBO.

parameter was estimated for each of the doses for which the parameter was measured. The sponsor then calculated the proportion of patients at 3 time points (first night, end of 1 month and end of 3 months) likely to have a clinically significant effect (that is, target values) for each of the assessed parameters.

These target values were used by the sponsor as general guidance around responses likely to provide benefit to the patients. They were based on an amalgamation of trial data and product label information from approved insomnia drugs and expert input. The sponsor then performed a literature review to confirm that in most cases these targets fall in the lower range of responses reported for approved sleep medications.

At Week 1 mean difference from placebo in change from baseline in subjective total sleep time was 23.7 minutes for suvorexant HD, and 15.0 minutes for LD. Mean subjective TST improved in all 3 treatment groups over the course of the study but difference from placebo for each dose group of suvorexant remained statistically significant until Month 6. At that time point only the HD suvorexant was superior to placebo. At the 6 month time point the mean change from baseline in sTST was 52.9 minutes for suvorexant LD, 66.7 minutes for suvorexant HD and 49.1 minutes for placebo.

Safety

A total of 2027 patients with primary insomnia (1198 non-elderly and 829 elderly patients) were exposed to any dose of suvorexant in the clinical development program for suvorexant. Of these, 1784 were treated with suvorexant in the Phase III trials and received doses from 15 mg to 40 mg. Some 1218 patients received suvorexant for at least 3 months, including 290 who received the currently proposed starting dose of suvorexant and 927 who received the initially proposed starting dose. 507 patients received suvorexant for 6 months or longer (42 on the current initial dose and 464 the previously proposed initial dose). No patients received the proposed starting dose for 12 months and 160 patients received the initially proposed starting dose for 12 months or longer.

Safety was thoroughly examined within the studies performed and included assessments of adverse events by dose (HD and LD), age, race and duration of treatment groups. Events of clinical interest associated with hypnotic agents were considered for the whole clinical trial program.

The primary safety group for analysis was the 0 to 3 months group from Studies P028, P029 and P009. Study P009 was the only study with safety and tolerability data to 12 months. This was a randomised, double-blind study comparing suvorexant HD and placebo. The most common (>2%) AEs more frequent in subjects given suvorexant in the Phase III group were somnolence (10.7% and 6.7% for suvorexant HD and LD respectively and 3.0% for placebo) and fatigue (3.8% and 2.2% for suvorexant HD and LD respectively and 1.8% for placebo). Adverse events in the Psychiatric Disorders system and Nervous System organ classes (SOC) category were reported more often by patients treated with suvorexant but apart from the above events no other single adverse events were notably different across the study groups.

Across all study groups, suvorexant did not cause QT prolongation or alter vital signs or measures of kidney and liver function.

Adverse events of special interest included suicidality, abnormal sleep behaviours, cataplexy, traffic accidents, withdrawal effects, residual effects (discussed in the PD studies) and abuse potential. Suicidal ideation and behaviours appear to be associated with suvorexant and to be dose-related. For the 0 to 3 months period in Studies P009, P028 and P029 there were 5/1291 subjects given HD suvorexant reporting these events compared with 1/493 given LD suvorexant and 1/1025 given placebo. During the 0-12 month interval for those studies, suicidal ideation was reported for eight patients on suvorexant HD (0.6%) and none given placebo. These figures identified by the Delegate

were from AE reporting only. The sponsor subsequently identified 3 additional cases from Columbia Suicide Severity Rating Scale (CSSRS) reporting forms that had not been reported as AEs occurring in Months 0 to 3 of the studies. The sponsor has noted that some of these patients had experienced suicidal ideation or similar events prior to receiving study medication. It was not clear whether there was a similar proportion of subjects given placebo with a history of suicidal ideation enrolled in the studies.

There were 2 reports of complex sleep-related behaviours in the Phase III studies and none in other studies. These both occurred in subjects given suvorexant HD. The first AE was a single event of somnambulism in a non-elderly patient. Another AE occurred in an elderly patient with a past history of talking in his sleep, who experienced a parasomnia (talking in his sleep and getting out of bed while asleep) while undergoing the Month 3 PSG assessment in the sleep lab. This patient also reported a second AE of somnambulism during the post study follow-up, 2 weeks after his last dose of suvorexant HD.

Hypnagogic/hypnopompic hallucinations were reported by 2 subjects given suvorexant LD and by 3 given HD in the 0 to 3 month Phase III study group. In the 0 to 12 months for Phase III studies an additional 2 reports (1 hypnagogic and 1 hypnopompic) were reported in the suvorexant HD group. No hypnagogic/hypnopompic hallucinations were reported in subjects given placebo. In the Phase I and II studies an additional 3 hypnagogic/hypnopompic hallucinations were reported in 3 elderly subjects given suvorexant 40 mg. There were no reports of cataplexy. (from sponsor's *Integrated summary of safety*). Falls were assessed as part of the investigation into a possible association between cataplexy and suvorexant but there was no increase in frequency in any of the treatment comparisons.

In subjects who drove during the studies, motor vehicle accidents (MVAs) were reported in 1/ 342(0.3%) subjects given suvorexant LD, 3/891(0.3%) given suvorexant HD and 4/692 (0.6%) given placebo. The AEs associated with these MVAs were contusions and musculoskeletal injuries. In all instances except one, the patient was the victim of another driver or swerved to avoid an accident. There was an additional MVA in Study P006 in a subject given placebo. Similarly there was no association between use of suvorexant and citations for traffic violations. There was no signal for an increased risk of falls in subjects given suvorexant, though this was considered by ACSOM.

An analysis of withdrawal effects based on responses for the Tyrer Withdrawal Symptom Questionnaire (WSQ) during the Run-out Phase was performed for the Combined Phase III Population by time point. For that analysis withdrawal was defined as emergence or worsening on 3 or more items on the WSQ on a night of the first three nights of the Run-out Phase. There was no relationship between emergence of withdrawal symptoms and abrupt cessation of suvorexant assessed during the 3 nights immediately after either abruptly ceasing suvorexant HD or LD.

Clinical evaluator's recommendation

The clinical evaluator was unable to recommend approval of the following indication:

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

The data presented in the submission are supportive of efficacy, at the proposed amended dosing recommendations, for treatment duration of up to 3 months. In addition, all the clinical trials were for primary insomnia, hence this should be reflected in the indication.

The clinical evaluator would have no objection to the approval of suvorexant for the indication:

Rivuley/Silumbra/Vispli/Belsomra is indicated for the short term (up to 3 months) treatment of primary insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Risk management plan

The Risk Management Plan has not been resolved to the satisfaction of the RMP evaluator. The following issues remain to be reconciled between the OPR and the sponsor:

- Appropriate additional pharmacovigilance activities should be conducted to investigate the potential use of suvorexant as a depressant ('downer') or existing appropriate additional risk minimisation activities should be assigned.
- Appropriate additional pharmacovigilance activities should be conducted to investigate the use in polypharmacy to evaluate the effect of interactions, such as falls in the elderly, or existing appropriate additional risk minimisation activities should be assigned.
- Appropriate additional pharmacovigilance activities should be conducted to investigate safe concomitant psychiatric drug use (other than paroxetine), or existing appropriate additional risk minimisation activities should be assigned.
- The sponsor should consider conducting additional pharmacovigilance activities to address residual effects further, particularly effects on driving and operating machinery.
- In order to assess drug misuse and diversion the sponsor should conduct a post authorisation surveillance study in Australia.
- The indication should be restricted to use in primary insomnia up to three months only, i.e. no use in secondary insomnia, and no long-term use.
- This submission was discussed by the ACSOM and a summary of the issues of concern to ACSOM was included in the RMP evaluation report and the advice provided by ACSOM was included in the final RMP evaluation report.

Risk-benefit analysis

Delegate's considerations

The issues raised in this discussion were provided to the sponsor soon after the final clinical evaluation report. The sponsor has provided responses to these concerns in a document that was provided to the TGA's Advisory Committee on Prescription Medicines (ACPM).

Suvorexant has a C_{max} of around 2 hours, an elimination $t_{1/2}$ of around 11 hours, takes about 3 days to reach steady state, has non-linear kinetics and potential for multiple CYP3A4 drug interactions for which the clinical impact could be quite serious, particularly for antidepressants and antipsychotic medications. This PK profile is not ideal for a hypnotic agent because of the potential for ongoing effect during waking hours and unpredictable effects if taken with other medications.

The sponsor responded to this concern by stating to the effect that because of the orexin antagonist mechanism factors beyond classic PK principles need to be considered in the evaluation process. The sponsor contends that the clinical next-day residual effects data support that most patients will not experience residual effects.

The proposed indication for suvorexant is quite broad in that it was proposed that suvorexant be indicated for insomnia without specifying the type of insomnia (for example, transient, acute, chronic) or cause (that is, primary or secondary) and does not include a duration of use or patient group in whom the product would be used. The sponsor responded to this concern by stating to the effect that the data supported no restriction in the duration of treatment for patients with insomnia. With regard to the type of insomnia (primary versus secondary) the sponsor has noted that insomnia is a heterogeneous disorder with a variety of inputs resulting in the final common pathway of unwanted wakefulness. The sponsor has also highlighted that the term 'primary insomnia' is not included in the newly revised DSM-V and a restriction to primary insomnia would be inconsistent with the nomenclature used for other hypnotics such as zolpidem.

The sponsor amended the initially proposed dose regimen of suvorexant to 20 mg/15 mg for under and over 65 year olds respectively. This amendment occurred after the pivotal studies were performed and analysed. Those studies were designed to demonstrate efficacy of the high dose regimen that is no longer the intended initial dose (40 mg/30 mg for under and over 65 years respectively). The primary analysis in those studies was only of efficacy measures associated with the high dose regimen. Some secondary efficacy measures included assessments of the low dose regimen but these were only for the baseline to Week 1 and baseline to the first night of randomised treatment. All other analyses (including 3 month efficacy measures) were exploratory for the low dose regimen.

Further analysis of efficacy of the HD and LD suvorexant regimen was subsequently performed using pooled data from the pivotal studies. That analysis supports efficacy of the currently proposed initial dose of 20 mg for adults aged <65 years and 15 mg for those aged ≥65 years. The mean improvements in the primary efficacy criteria of subjective TST were modest with difference from placebo in change from baseline in subjective mean total sleep time of around 16 minutes for LD suvorexant and 22 minutes for HD suvorexant. There was a clear trend towards improved subjective TST in all groups regardless of treatment over time. At Month 6 there was no statistically significant difference in change from baseline in subjective TST between 20 mg suvorexant and placebo. Thus long term efficacy of the 20 mg dose of suvorexant has not been demonstrated.

The sponsor responded to the above summary of results by representing summary data and by summarising the exploratory endpoints of the Insomnia Severity Index and the Patient-and Clinician Global Impressions scales. Both these assessments showed a statistically significant benefit from suvorexant at either high or low dose relative to placebo at Months 1 and 3 for the pooled P028 and P029 populations. The Delegate does not dispute that either dose of suvorexant results in increases in objective and subjective measures of sleep up to 3 months. The extent of improvement was modest, the analysis was exploratory and the effect was not maintained beyond 3 months. The Delegate also notes inconsistency between the proportion of subjects rated as having clinically meaningful responses between Month 1 and 3 in all treatment groups. In all treatment groups clinically meaningful responses increase over time. If the statistics on this exploratory endpoint are accepted, around 12% of patients obtained a clinically meaningful benefit from suvorexant above what was achieved from placebo.

While short term efficacy of the proposed initial dose regimen for healthy adults has been demonstrated there are significant areas of safety concern. These are:

- Somnolence the day after dosing. This is particularly important when considering that many people need to drive and will drive even when they are aware they are sleepy. Impaired ability to drive consistent with that of a blood alcohol of 5 g/L was present in 22% of subjects the day after they were given 20 mg suvorexant in Study P035. The effect on individuals taking other medications that can affect ability to drive or with

pre-existing medical conditions affecting ability to drive was not assessed but can reasonably be expected to be greater than observed in this study. That the recommended dose of zopiclone had a greater effect on ability to drive is also of concern but is not the subject of this submission. The effect of all hypnotics on next day ability to drive is clearly a safety issue.

- Suicidal ideation occurred in excess in patients receiving suvorexant in a dose-dependent manner though patients who would be considered at risk for this adverse event were excluded from studies. Exclusion criteria for the pivotal studies included but are not limited to: history of an Axis 1 or II disorder; signs or symptoms of depression; shift work; history of narcolepsy, cataplexy, circadian rhythm sleep disorder, parasomnia (including nightmare disorder, sleep terror disorder, sleepwalking disorder and REM behaviour disorder), sleep-related breathing disorder, periodic limb movement disorder or restless legs syndrome. Whether suicidal ideation would be more frequent in individuals with those conditions has not been assessed.
- Abnormal sleep behaviours also occurred in a dose-dependent manner in a population selected to have no history of these behaviours. Suvorexant has not been assessed in individuals with any of those conditions or a history of those conditions. In addition, the effect of alcohol combined with suvorexant on abnormal sleep behaviours is not known.
- Suvorexant is metabolised predominantly via CYP3A4 and plasma concentrations are substantially altered by CYP3A4 inhibition. Suvorexant should not be taken with moderate or strong CYP3A4 inhibitors.
- The effect of 40 mg suvorexant in patients with mild to moderate sleep apnoea been assessed and a mean increase compared with placebo in AHI of 2.66 on Day 4 was observed. This effect is likely to be more severe in patients with more severe sleep apnoea and if suvorexant is taken with concomitant medicines that are associated with respiratory depression. However this has not been assessed.

The sponsor responded to the concern about ability to drive the day after dosing by stating that, with reference to Study P035 (a non-elderly car driving study), the SDLP difference versus placebo of ≥ 2.4 cm used as the primary endpoint in this study represents a 'threshold for mean' rather than an individual threshold for impairment and that changes of that magnitude are seen with placebo-placebo rest-retest data. The test therefore does not reliably indicate drug-induced impairment. While the Delegate agrees that this may be the case and perhaps there is no adequately validated surrogate for effect of a drug on driving ability, the sponsor has now not adequately examined the safety of driving after taking suvorexant.

Data from the Phase III studies on vehicle citations and accident rates are insufficient to determine safety of suvorexant on driving because vehicle accidents are not common and thousands of subjects would need to be followed for many months to show statistically significant differences in accident rates.

The sponsor responded to concerns about suicidality by noting that there were no instances of suicidal behaviour and that the suvorexant clinical development program is one of the first hypnotic development programs to prospectively assess suicidal ideation and behaviour. In addition the total number of events of suicidal ideation was low, the events were transient and of mild to moderate intensity and not associated with intent or action. The events also occurred in the presence of confounding factors, including pre-existing and/or current depression, a history of suicidal ideation or clear external precipitants. Additionally there was more person-time of exposure to suvorexant than to placebo.

The sponsor's response to the contention that suvorexant was associated with abnormal sleep behaviours was to concentrate on the 2 reports of parasomnias in patients taking suvorexant. The reports of hypnagogic/hypnopompic hallucinations which were associated with suvorexant were not discussed. The sponsor considers labelling would appropriately address abnormal sleep behaviours.

The sponsor's response to the contention that suvorexant should not be taken with moderate or strong CYP3A4 inhibitors was to contest that serious adverse effects were not dose-related and that interactions are predictable and manageable through product labelling. The Delegate agrees there was no clear linking of the total number of serious adverse events with dose. The Delegate remains concerned that suicidal ideation, abnormal sleep behaviours and effect on ability to perform fine motor functions and to drive motor vehicles will be dose-related and influenced by concomitant medicines that inhibit the metabolism of suvorexant.

The sponsor responded to concerns that suvorexant, if taken by individuals with sleep apnoea would reduce oxygen saturation by noting that changes in the AHI (apnoea-hypopnoea index) were small and there was large between-subject and within-subject variability on the AHI endpoint. In healthy subjects no changes in AHI occurred.

Summary of issues

- The population in whom suvorexant is proposed to be is broader than the population in whom efficacy and safety was assessed.
- The long half-life of suvorexant results in blood levels the morning after dosing that are similar to those which are intended to be therapeutic at night. The sponsor contends that due to the novel mechanism of action of suvorexant, factors beyond classic PK principles need to be considered in the evaluation process and that clinical next-day residual effects data support that most patients will not experience residual effects.
- Efficacy was quite modest, assessed by objective and subjective measures and has not been demonstrated to persist beyond 3 months yet the sponsor proposes long term use.
- Safety issues include next day ability to drive, abnormal sleep behaviours, suicidality, effect on individuals with sleep apnoea and the effect of concomitant medicines such as antipsychotics, opioids and antidepressants.

Proposed action

The Delegate is not in a position to say, at this time, that the application for suvorexant should be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider that the safety risks of suvorexant are predominantly dose-related?
2. Can the committee identify a patient group in whom the risks from use of suvorexant are acceptable, given the demonstrated extent of benefit?
3. Should suvorexant be contraindicated in patients with psychiatric disorders such as anxiety or depression, and in patients known to abuse illicit drugs or alcohol due to the unknown effects of suvorexant on individuals with pre-existing risk factors for

suicidality and the lack of information on concomitant effects of suvorexant and medications to treat these conditions?

4. Has the propensity of suvorexant to cause dependency been adequately explored?
5. Does the committee consider that suvorexant, at the dose regimen proposed could be used to treat insomnia for up to 3 months in individuals with no history of psychiatric illness?
6. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Merck Sharp & Dohme (MSD) notes that at the time the Delegate was not in a position to say that the application for suvorexant should be approved for registration. MSD maintains that the benefit/risk assessment remains favourable to support the registration of suvorexant for '*treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance*'. The patient should be initiated with the 20/15 mg dose and for those patients whose symptoms (onset and/or maintenance) persist and who do not experience next day somnolence or other residual effects, a dose increase to 40/30 mg may be considered as clinically appropriate.

Background

Suvorexant is the first orexin receptor antagonist (ORA) to successfully complete development for the treatment of chronic insomnia, with evidence for long term efficacy, safety, and tolerability. Orexin receptor antagonism represents a novel approach and a new treatment option for patients with insomnia. The orexin neuropeptide signaling system is a central promoter of wakefulness. Suvorexant is chemically unrelated to benzodiazepines, non-benzodiazepine hypnotics, barbiturates or other drugs with hypnotic properties. Suvorexant has no pharmacological affinity for receptors that bind to GABA, serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine or opiate receptors.

Estimates of the prevalence of insomnia are consistently around 15%. Insomnia is a primary disorder, often exhibiting evidence of a state of hyperarousal, and warrants treatment independent of (or in addition to) treatment of comorbid conditions (DSM-V). Chronic insomnia is associated with increased risk for other important disorders including depression, hypertension and diabetes. Currently available agents for the treatment of insomnia are limited (most work through global effects on the GABA system), and few have a balanced clinical profile with respect to sleep onset and maintenance.

Efficacy

The tools available to assess insomnia include bioassays of how patients spend their time during the intended sleep period, specifically objective polysomnography (PSG) and subjective patient questionnaire recall of endpoints intended to assess sleep onset and sleep maintenance efficacy, as well as scales such as the Insomnia Severity Index (ISI). The delegate states '*Efficacy was quite modest, assessed by objective and subjective measures and has not been demonstrated to persist beyond 3 months yet the sponsor proposes long term use.*'

However, as shown in the data presented below, objective and subjective effects were robust, and in the long-term study the improvements at 3 months were sustained in subsequent assessments for the full 12 month period.

Confirmatory efficacy: In replicate 3 month pivotal trials (P028 and P029), suvorexant 40/30 mg (high dose [HD]) and 15/20 mg (low dose [LD]) demonstrated substantial improvements in both objective (Figure 3a) and subjective (Figure 3b) measures of sleep

onset and sleep maintenance in patients with chronic insomnia. Likewise, total sleep time (TST), a global sleep endpoint that measures the sleep time across the night was substantially improved based on objective (TST) and subjective (sTST) measures. At Month 3, suvorexant increased TST by 75-80+ minutes from baseline, while sTST increased 55-60+ minutes, with differences from placebo as shown below (Table 24).

Figure 3 a and b. Objective (a) and subjective (b) measures of sleep onset and sleep maintenance.

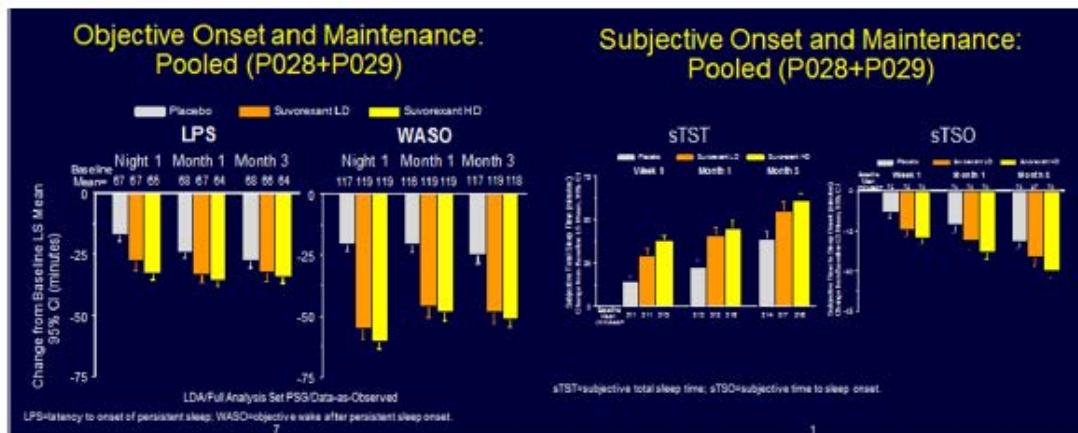


Table 24. Summary of Objective and Subjective TST Improvements Compared to Baseline (and to Placebo) at Month 3 for suvorexant

	Suvorexant 40/30 mg (HD)*	Suvorexant 20/15 mg (LD)
Subjective TST	>60 minutes (22 min vs. placebo)	~55 minutes (16 min vs. placebo)
Objective TST	>80 minutes (33 min vs. placebo)	>75 minutes (27 min vs. placebo)

*HD = high dose regimen, non-elderly/elderly, LD = low dose regimen, non-elderly/elderly

The clinical relevance of these effects was mirrored by the improvements in suvorexant treated patients over those treated with placebo across numerous patient and clinician rated scales (all nominal p-values <0.05), which included assessments of sleep quality, how refreshed patients felt on waking as part of the Insomnia Severity Index (ISI), and Patient and Clinician Global Impressions of Severity and Improvement.

Of particular importance are the results of the ISI, a validated and widely used 7-item global composite patient-reported measure. Of the seven individual ISI scale items (falling asleep, staying asleep, early awakening, satisfaction, interference, noticeable, and worry), four items assess waking functionality rather than sleep symptoms. In this regard, the ISI is complementary to the standard registration endpoints and bridges from improvement in sleep symptoms to other important functional domains relevant to patients.^{20,21,22} Defining a responder by a ≥6-point improvement from baseline in ISI total score²¹, the proportion of patients in the pooled pivotal trials (P028+P029) who experienced a clinically meaningful improvement was higher in both the suvorexant 40/30 mg and 20/15 mg treatment groups than in the placebo group, with a nearly 2 fold increase over placebo in the odds ratio of response for both suvorexant 40/30 mg and 20/15 mg at Month 1 and at Month 3 (all p-values <0.05).

²⁰ Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*; 2001;2(4):297-307.

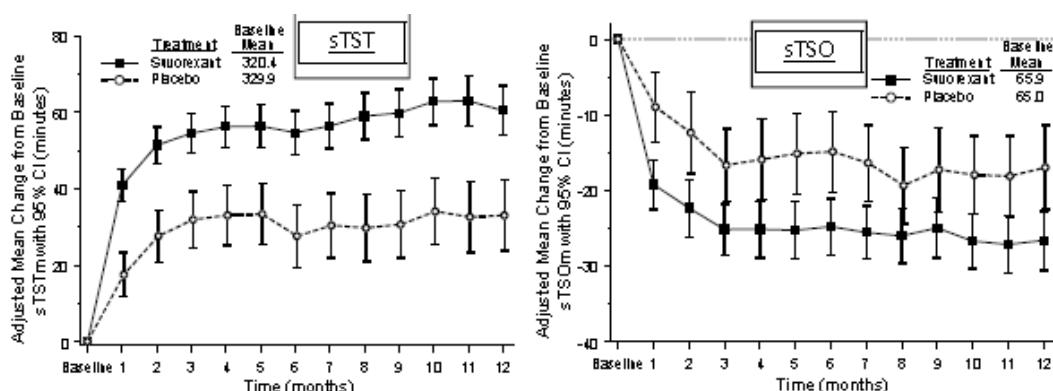
²¹ Yang M, Morin CM, Schaefer K, & Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. *Curr Med Res Opin*; 2009;25(10):2487-94

²² Morin CM, Belleville G, Bélanger L, & Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*; 2011;34(5):601-8.

Taken together these results provide strong evidence that the changes in sleep onset and sleep maintenance associated with suvorexant translate into noticeable, beneficial clinical improvement valued by patients and their care providers.

Long term efficacy: The long term efficacy of suvorexant 40/30 mg was evaluated in a year-long placebo-controlled nightly dosing study (P009) in 779 treated-patients with chronic insomnia, which to our knowledge is the first such study of its kind. This study was designed to include those who met DSM-IV criteria for insomnia with as limited exclusions as possible, and thus to model as closely as possible expected real world outpatient use. Protocol pre specified exploratory analyses demonstrated treatment differences favouring suvorexant at every month throughout the 12 month treatment period for both sleep onset and sleep maintenance (Figure 4).

Figure 4. Study P009. Adjusted (LS) means and 95% CI for change from baseline in mean sTST and sTSOM (minutes) for suvorexant HD versus placebo by month treat phase (LDA/Full Analysis Set/Data-as-Observed)



Positive results were also observed for other patient-reported assessments of sleep and insomnia. During the 2 month Randomized Discontinuation Phase of this 12 month trial (P009), patients who continued to be treated with suvorexant demonstrated sustained benefit compared to those whose treatment was discontinued, providing further evidence of the long-term benefit of suvorexant treatment. Importantly, abrupt discontinuation of suvorexant in this study showed little risk for withdrawal or clinically important rebound effects.

The efficacy of both the suvorexant 40/30 mg and 20/15 mg regimens has been demonstrated for the 3 month primary endpoint in the two replicate efficacy trials P028 and P029. The consistency of response shown for both 40/30 mg and 20/15 mg in the pooled P028+P029 analysis of the Full Analysis Set through Month 6 which included the 3-month duration extension phase of P028, provide indirect but compelling evidence that the efficacy of the 20/15 mg dose regimen is also sustained similar to that of suvorexant 40/30 mg in the setting of chronic use. During periods up to 6 months the efficacy for the 20/15 mg dose behaves similarly to that of 40/30 mg, and there is no biological reason to expect a sudden divergence to emerge between the two doses in later months. Importantly, no other available sleep medications in Australia have provided controlled evidence for efficacy beyond 3 months; given that many patients require chronic treatment, the long-term efficacy of suvorexant addresses a currently unmet need for insomnia patients.

Safety

The Delegate states '*Safety issues include next day ability to drive, abnormal sleep behaviours, suicidality, effect on individuals with sleep apnoea and the effect of concomitant medicines such as antipsychotics, opioids, and antidepressants*'. A comprehensive assessment of safety was performed in the suvorexant development program, in which key elements included evaluations of potential for next day effects, suicidality, drug

interactions, and risk of dependency. The data obtained demonstrates that suvorexant is generally well tolerated at the recommended doses by the majority of patients, with risks that can be managed through product labeling and a robust post-marketing pharmacovigilance.

Next day residual effects. somnolence reporting

The majority of patients studied in the Phase III trials did not report somnolence but a dose-related effect was observed for the minority who did (Figure 5) and this effect was time limited.

The severity of somnolence was generally mild-to-moderate and did not require treatment cessation or dose adjustment. In most cases, occurrence of somnolence was reported within the first week after initiating treatment and resolved spontaneously without medication interruption, with few events of somnolence reported after one month of treatment. Adjusted rates of somnolence reported in trials of patients taking suvorexant were comparable to the commonly used modern non-BZD hypnotics, zolpidem CR and eszopiclone (Table 25). This comparability in somnolence reporting rates despite the shorter elimination half-lives of the non-BZD hypnotics (approximately 3 to 6 hours) relative to that of suvorexant (approximately 12 hours), speaks to the uniqueness of the ORA mechanism with respect to risk of next day effects.

Figure 5. Incidence and severity of somnolence combined Phase III population 0-3 months (P028, P029, P009) (All patients as treated)

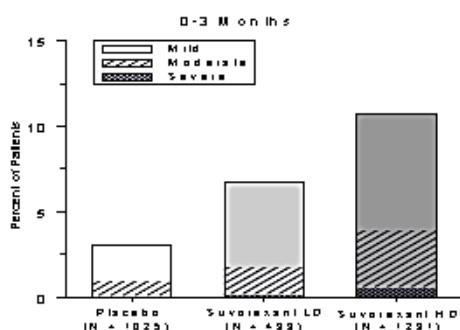


Table 25. Reported next day somnolence on suvorexant is comparable to other modern hypnotics

- The frequency of somnolence reported by patients taking suvorexant is comparable to shorter-acting drugs that have less pronounced effects on sleep maintenance

	Somnolence (increase above placebo non-elderly, self-report)	
	Low Dose	High Dose
Suvorexant* (3 weeks, 20 mg, 40 mg)	5%	8%
Zolpidem CR† (3 weeks, 12.5 mg)	N/A	13%
Suvorexant* (6 weeks, 20 mg, 40 mg)	5%	9%
Eszopiclone‡ (6 weeks 2 mg, 3 mg)	7%	5%

* Kaplan-Meier estimates from pooled Phase 3 data. † Data from Lunesta® (eszopiclone) package insert. ‡ Data from Ambien CR® (zolpidem tartrate extended-release) package insert.

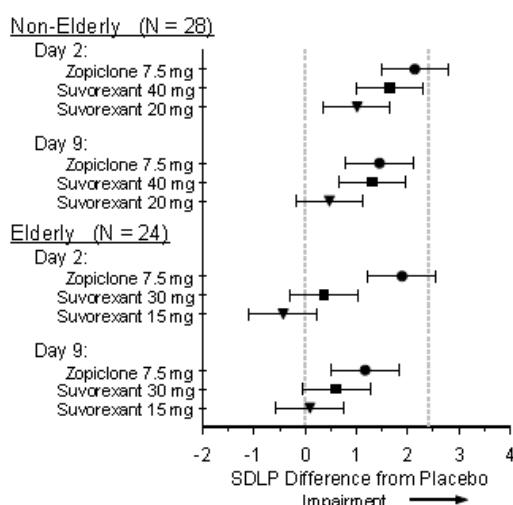
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Driving Studies: The sponsor is responding to the Delegate's statement that the '... sponsor has not adequately examined the safety of driving...'. The sponsor has adequately examined the safety of driving in two methods, first an on-the-road driving study, and also a prospective evaluation of citations and accident reports in Phase III studies (provided in the Response to the Delegate). The sponsor's interpretation of the car driving studies (non-elderly [P035] and elderly subjects [P039]) follows and the two points below are fundamental in understanding the data:

1. The mean change in standard deviation of lane position relative to placebo (mean SDLP, a measure of "weaving") is the primary validated outcome measure of population risk. It has exhibited repeated sensitivity to a number of drugs, including hypnotics such as zopiclone and CNS depressants such as alcohol.
2. The threshold used to define "driving impairment" is a mean increase in SDLP relative to placebo of 2.5 cm (2.4 cm in the Sponsor studies). This threshold is defined by the mean effect in the treated group produced by driving with a blood alcohol concentration (BAC) of 0.05%. It is not a validated threshold measure of an individual driver's increased risk of an automobile accident.²³

The sponsor's primary assessment is based on the mean analysis consistent with the key points above. In both non elderly and elderly subjects, there was no clinically meaningful effect on next-day driving performance in the population treated at any dose level with suvorexant (15/30 mg or 20/40 mg) since the 90% confidence intervals for the mean treatment difference (suvorexant versus placebo) for SDLP were <2.4 cm. These data are displayed in Figure 6.

Figure 6. SDLP Differences from Placebo (Mean \pm 90% Confidence Interval) (cm) Following Single Dose (Day 2) and Multiple Doses (Day 9) of Suvorexant in Healthy Non-elderly and Elderly Subjects (vertical dotted line at 2.4 cm indicates the prespecified clinical significance bound)



The sponsor's secondary assessment was the symmetry analysis (Table 23 above) and should not be considered as an 'outlier analysis' of individual subject driving impairment. It represents a population level analysis of whether there is a shift in the distribution of responses. This analysis cannot be used to conclude that any individual with a change greater than 2.4 cm is impaired as the Delegate has asserted. This is also evidenced by some subjects having a change of this magnitude or greater following administration of only placebo before two separate drives in (provided in the February 2014 Response to the Delegate).

In summary, as part of the comprehensive assessment of residual effects, the sponsor believes that the multiple dose on-the-road driving studies in the elderly and non-elderly sufficiently evaluated the driving safety risks in relevant populations. While there was no clinically meaningful impairment of next-day driving performance based on the mean analysis for all doses (15 to 40 mg), the symmetry analysis of SDLP did reveal statistically

²³ Verster JC, & Roth T. Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP) Int J Gen Med; 2011; 4:359-71

significant effects in the non-elderly. The sponsor recognises that some individuals may be more sensitive to the residual effects of suvorexant on driving ability.

The sponsor believes that any safety concerns with respect to driving performance can be addressed through product labelling and robust pharmacovigilance.

Patient populations studied

The Delegate states '*The population in whom suvorexant is proposed to be used is broader than the population in whom efficacy and safety was assessed*'. The development program was intended primarily to characterize the efficacy and tolerability of suvorexant in patients with insomnia (predominantly chronic insomnia). The exclusion of conditions noted by the Delegate from suvorexant trials was based on the underlying sleep disruption associated with these conditions and thus the potential for confounding treatment effects, not due to safety concerns specific to the potential use of suvorexant in these populations. The regulatory guidance for clinical investigation of hypnotic medicinal products requires that a homogenous patient population is studied where confounding factors are removed, hence the inclusion of patients with primary insomnia in the confirmatory clinical trials (P028 and P029). However, patients with past histories of major depression or depression controlled on treatment were eligible and participated in the long-term safety Study P009.

The suvorexant program was one of the first hypnotic development programs to systematically use the Columbia Suicide Severity Rating Scale (C-SSRS) surveillance methodology to assess suicidal ideation prospectively, and comparative data to other hypnotics are lacking. During the three Phase III trials suicidal ideation was reported for 1 (0.1%) patient on suvorexant 20/15 mg, 9 (0.7%) patients on suvorexant 40/30 mg, and 1 (0.2%) patient on placebo. The majority of these events was transient, with the majority lasting minutes to hours, were mild to moderate in intensity, and were not associated with active intent or action. All occurred in the context of factors typically associated with increased risk for suicidal ideation (such as history of depression, acute stressors). Even though a highly sensitive and systematic method of monitoring for suicidal ideation (that is, C-SSRS) was used in the program, the absolute number of ideation events across all groups was low, and consistent with the number of events that might be expected, given the ubiquity of suicidal ideation as a transient symptom in the general population. For example, the 12 month exposure-adjusted rate of suicidal ideation in the combined Phase III Population was 0.6%, which is in line with 12 month prevalence rates of 2-4% reported in the general adult population.^{24,25,26} There was no temporal pattern suggesting an association with drug (that is, events occurred at various times during the study, and events were not associated with starting or stopping treatment, or with any particular duration of treatment). In those patients who continued in the study, the events resolved despite continuing treatment with study drug. Finally, as assessed by the Quick Inventory of Depressive Symptoms, there was no evidence that suvorexant was associated with deleterious general effects on mood or anxiety that could have increased risk for suicidality. Thus the overall weight of evidence suggests that the risk of suicidal ideation is low, consistent with expected background rates, and the small treatment imbalance is unlikely to represent a causal association with suvorexant.

²⁴ Kessler RC, Berglund P, Borges G, Nock M, & Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA*;2005;293(20):2487-95

²⁵ Borges G, Nock MK, Haro Abad JM, Hwang I, Sampson NA, Alonso J, Andrade LH, Angermeyer MC, Beautrais A, Bromet E, Bruffaerts R, de Girolamo G, Florescu S, Gureje O, Hu C, Karam EG, Kovess-Masfety V, Lee S, Levinson D, Medina-Mora ME, Ormel J, Posada-Villa J, Sagar R, Tomov T, Uda H, Williams DR, & Kessler RC. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J Clin Psychiatry*; 2010;71(12):1617-28

²⁶ Crosby AE, Han B, Ortega LA, Parks SE, & Gfroerer J. Suicidal thoughts and behaviors among adults aged ≥18 years--United States, 2008-2009. *MMWR Surveill Summ*; 2011;60(13):1-22.

Nonetheless as patients with insomnia are a population at increased risk for suicidal ideation irrespective of treatment, as with other sleep medications, patients and physicians should be aware of the possibility that suicidal ideation may emerge during treatment. The Sponsor plans to address this risk through appropriate class labelling and robust pharmacovigilance.

Concomitant use - Moderate CYP3A4 inhibitors

As explained in the Response to the Delegate, consistent with CYP3A mediated biotransformation of suvorexant, drug-drug interactions via CYP3A affecting suvorexant pharmacokinetics have been observed; however, the magnitude of these interactions are predictable and are manageable through product labeling and robust pharmacovigilance. Polypharmacy with strong or moderate CYP3A inhibitors, such as treatments for hepatitis C, HIV or systemic fungal infections is not common in the intended population of insomnia patients. In consideration of the revised dosing recommendations submitted to TGA, a daily dose of suvorexant co-administered with strong CYP3A inhibitors cannot be recommended. However, moderate CYP3A inhibitors do not inhibit CYP3A as strongly and have lesser effects on suvorexant exposures (2.05 times increase). The lower dose strength of 15 mg of suvorexant would mimic exposures, when co-administered with moderate CYP3A inhibitors, to those reported following administration of 30 mg administered alone (elderly) and reduced exposures to 40 mg administered alone (non-elderly).

Therefore, the lowest dose strength of 15 mg suvorexant when co-administered with moderate CYP3A inhibitors is an appropriate dose for both elderly and non-elderly patients with general cautionary language provided informing health care providers of the potential for higher suvorexant concentrations and hence, increased potential for next-day residual effects. In consideration that exposures will be within those already observed, AEs are expected to be consistent with those reported.

Dependency (topic for delegate question 4)

Tolerance and/or withdrawal can be indicative of risk for physiological dependence (DSM, ICD), and both aspects of dependence risk were evaluated in the suvorexant Phase III clinical program. The results show that suvorexant was not associated with either the development of tolerance when administered for up to 1 year, or with withdrawal following abrupt treatment cessation, together indicating a low risk for dependence.

The assessment of tolerance included tracking of treatment compliance and the potential for study medication misuse or diversion, which was evaluated at each study visit through pill counts and collection of additional information to characterise events. Of the few cases in which discrepancies occurred, the majority were isolated accidental events in which patients lost study medication and/or denied taking additional study medication, with no pattern suggestive of abuse. Additionally, sustained levels of suvorexant efficacy in long-term studies with durations ranging from 3 months to 1 year also provide evidence that tolerance to suvorexant treatment does not occur.

The potential for acute withdrawal symptoms was systematically assessed during the Run-Out Phase of the Phase III trials, using both objective (Tyrer Withdrawal Symptom Questionnaire (WSQ)) and subjective (based on a predefined list of adverse events) measures. As summarized in the Delegate's report, there was no relationship between emergence of withdrawal symptoms and abrupt cessation of suvorexant during the first 3 nights immediately following cessation of treatment with suvorexant. In addition, no AEs associated with potential withdrawal were reported during the Run-Out Phase.

Recommendation 4 in RMP evaluation report

The sponsor should consider conducting additional pharmacovigilance activities to address residual effects further, particularly effects on driving and operating machinery.

Sponsor response:**3. The sample size:**

Based on the assumption made about within subject variability on the driving task when designing the car driving studies, the sample sizes selected provided sufficient power to meet the studies' objectives.

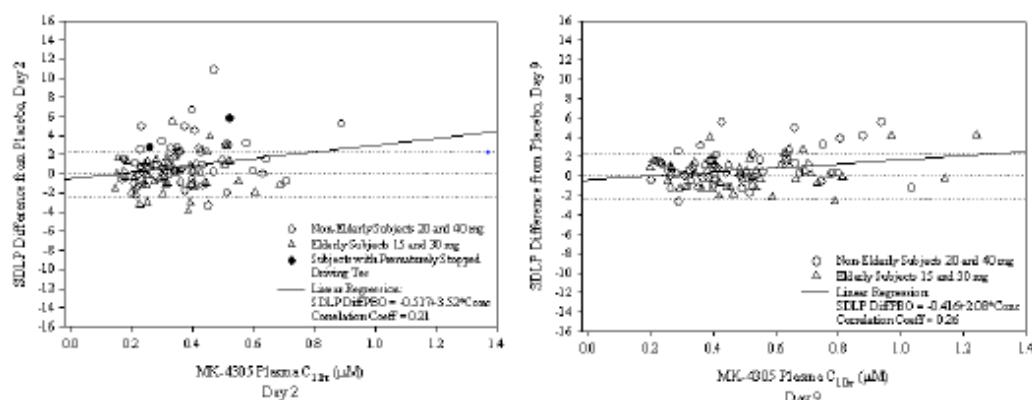
4. The 95% confidence interval:

Since the objective was to rule out an increase in SDLP relative to placebo of at least 2.4cm, a one-sided test at the alpha =0.05 level was chosen. The two-sided 90% confidence interval presented is consistent with this test as the upper bound represents a one-sided 95% confidence interval.

5. Correlation with suvorexant plasma concentrations:

In their submission (Effects of Suvorexant on Next-day Driving Performance) the sponsor has stated that plasma concentrations at 11 h postdose were measured in both driving studies and PK-PD relationship was explored for SDLP. There was an apparent dose response on SDLP (especially for the non-elderly study) but a very weak correlation between C11hr and treatment difference on SDLP as shown in Figure X. In the below figure, SDLP differences from placebo versus suvorexant plasma concentrations (C11hr) were shown for the non-elderly and elderly subjects for both Day 2 and Day 9 and subjects whose driving was prematurely stopped due to somnolence were also identified.

Figure. Weak correlation between suvorexant PK and SDLP does not fully explain SDLP changes or stopped drives.

**Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the delegate that Belvasom/Rivuley/Silumbra/Belsomra film coated tablets containing 15 mg, 20 mg, 30 mg and 40 mg of the new chemical entity, suvorexant, has an overall negative benefit-risk profile for the proposed indication.

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of suvorexant.

In making this recommendation the ACPM

- noted the proposed indication for suvorexant is quite broad in that it was proposed to be indicated for insomnia without specifying the type of insomnia (such as transient,

acute, chronic) or cause (that is, primary or secondary) and does not include a duration of use or patient group in whom the product would be used.

- noted the issues with pharmacology in that;
 - C_{max} is not reached for 2 hours, thus suggesting a long lag time to efficacy
 - elimination half-life is approximately 11 h suggesting potential for ongoing effect during waking hours which is demonstrated by the trial including a driving test
- expressed concern over the potential for multiple CYP3A4 drug interactions, especially problematic with antidepressants and antipsychotics.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the committee consider that the safety risks of suvorexant are predominantly dose-related?

The ACPM were of the view that the evidence presented suggested dose-related effects, including safety risks.

2. Can the committee identify a patient group in whom the risks from use of suvorexant are acceptable, given the demonstrated extent of benefit?

The ACPM advised there was no identifiable patient group in whom the risks were acceptable.

3. Should suvorexant be contraindicated in patients with psychiatric disorders such as anxiety or depression, and in patients known to abuse illicit drugs or alcohol due to the unknown effects of suvorexant on individuals with pre-existing risk factors for suicidality and the lack of information on concomitant effects of suvorexant and medications to treat these conditions?

The ACPM agreed all these patient groups could be at increased risk if also using suvorexant.

4. Has the propensity of suvorexant to cause dependency been adequately explored?

The ACPM was of the view the risk of dependency had not been adequately explored.

5. Does the committee consider that suvorexant, at the dose regimen proposed could be used to treat insomnia for up to 3 months in individuals with no history of psychiatric illness?

The ACPM advised against treatment in this population as it was a very difficult population to delineate and the safety risks have not been adequately defined, particularly in terms of continued effects the day after treatment (for example, the driving test).

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the application of suvorexant 15 mg, 20 mg, 30 mg and 40 mg film-coated tablets with the proposed indication:

For the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

This decision has been taken on the grounds that on balance the clinical benefit has not been sufficiently demonstrated to justify the risks from patient exposure in the proposed population group.

This decision is based on the evaluation of information and data provided with the original submission letter and with any subsequent correspondence and submissions relating to the original submission. In making this decision, the Delegate also considered the advice provided by the Advisory Committee on Prescription Medicines (ACPM) at its 297th meeting, that suvorexant has an overall negative benefit-risk profile for the proposed indication.

Reasons for decision

Firstly, suvorexant appears to result in a dose-dependent reduction in psychomotor performance on next-day testing, though this has not been fully explored. Psychomotor performance tests including Choice Reaction Time (CRT), Digit Symbol Substitution Test (DSST) and Simple Reaction Time (SRT) all deteriorated in a dose dependent manner in subjects given suvorexant. These psychomotor performance tests were included as exploratory pharmacodynamic endpoints in Study P002. In that study the effects of suvorexant on psychomotor performance were evaluated at 10 hours post dose.

Additionally, assessment of the effect of suvorexant on driving ability was conducted and those tests also suggested impaired or reduced day-time functioning in healthy adults given suvorexant at therapeutic doses compared with healthy adults given placebo.

Improved day-time functioning is listed as one of the basic efficacy criteria to be evaluated in clinical trials. It appears that for suvorexant improved day-time function has not been demonstrated and functioning is somewhat impaired in a dose-dependent manner in healthy people given suvorexant in clinical trials.

Secondly, while a degree of efficacy assessed using objective and subjective measures of sleep has been demonstrated for the proposed initial dose of suvorexant for up to 3 months of continuous treatment this is not sufficient to permit long term use of suvorexant as a hypnotic agent because the hypnotic effect appears to decrease over time. The most comprehensive assessment of efficacy was in the analysis of the pooled results from the dose-finding study and the two pivotal efficacy and safety studies (Studies P006, P028 and P029).²⁷ An assessment of change from baseline in subjective total sleep time (sTST) was performed. At Week 1 the mean difference from placebo in change from baseline in subjective total sleep time (sTST) was 23.7 minutes for suvorexant high dose, and 15.0 minutes for suvorexant low dose. Mean sTST improved in all 3 treatment groups over time but the difference from placebo for each dose group of suvorexant remained statistically significant only until Month 6. At that time-point only the high dose suvorexant was superior to placebo. At the 6 month time point the mean change from baseline in sTST was 52.9 minutes for suvorexant low dose, 66.7 minutes for suvorexant high dose and 49.1 minutes for placebo.

Thirdly, the efficacy demonstrated at any time-point is quite small in comparison with the changes that occurred over time. Patients in all treatment groups tended to have longer subjective total sleep time as the studies progressed. The efficacy attributable to suvorexant in those studies is arguably not clinically significant.

In the sponsor's Overall Response to the Delegate document submitted with the Pre ACPM response it was stated that dose-related somnolence was the most frequent adverse effect of suvorexant. In patients treated for up to 3 months in the 0 to 3 Month Combined Phase III population, the incidence of somnolence for suvorexant 15/20 mg, suvorexant 30/40 mg, and placebo was 6.7%, 10.7%, and 3.0% respectively. Given one of the purposes of a hypnotic agent is to improve next-day functioning the excess of sedation in patients taking suvorexant strongly suggests it does not improve next-day functioning but rather, for a significant minority of patients, suvorexant reduces next-day functioning by increasing sedation.

²⁷ Only Studies P028 and P029 were pooled.

Fourthly, suvorexant was associated with an increase in the proportion of patients reporting suicidal ideation compared with placebo treatment. This excess occurred in a dose-dependent manner and in a population in which patients who would reasonably be considered at increased risk for this event were excluded. Exclusion criteria for the pivotal studies included but are not limited to: history of an Axis 1 or II disorder; signs or symptoms of depression; shift work; history of narcolepsy, cataplexy, circadian rhythm sleep disorder, parasomnia (including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behaviour disorder), sleep-related breathing disorder, periodic limb movement disorder, or restless legs syndrome. Whether suicidal ideation would be more frequent in individuals with those conditions has not been assessed.

Fifthly, abnormal sleep behaviours occurred in a dose-dependent manner in a population selected to have no history of these behaviours. Suvorexant has not been assessed in individuals with a history of any complex sleep behaviour including somnambulism, parasomnia and hypnagogic/hypnopompic hallucinations or narcolepsy. If suvorexant were to be marketed it is likely that it would be taken by individuals with these conditions and in conjunction with alcohol, even though the Product Information and Consumer Medicines Information may include warnings against such use. The effect of alcohol combined with suvorexant on abnormal sleep behaviours is not known however it is appears to be a factor with similar complex sleep behaviours associated with other hypnotic agents.

While there are other risks associated with use of suvorexant, the Delegate does not consider they would be of sufficient severity to justify not approving suvorexant. These risks include the risk of high serum levels of suvorexant if individuals take suvorexant with medicines that inhibits its metabolism via CYP3A4 and the effect of suvorexant in patients with sleep apnoea, which may be undiagnosed or untreated.

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act.

Sponsor's appeal

The following is a summary of the sponsor's objections to the initial decision as described in the appeal Delegate's decision letter.

The sponsor contests that certain safety issues were given disproportionate emphasis and were 'assessed largely in reference to the safety profile observed with other currently available hypnotic medicines'.

The sponsor contests that the initial decision did not consider the comments provided in the sponsor's Pre-ACPM Response.

Demonstration of suvorexant safety

The sponsor notes that the initial decision-maker used the issues of potential for next-day impairment, suicidality and abnormal sleep behaviours as part of the grounds for rejection. The sponsor argues that these concerns 'can be managed through appropriate product labelling, consistent with the approach taken for other sedative/hypnotic drugs already approved in Australia, and through appropriate pharmacovigilance'.

Potential for next-day impairment that includes driving performance

The sponsor contests that the residual effects profile of suvorexant has been well-characterised and found acceptable for most patients at recommended doses.

The sponsor distinguishes between the safety measure 'next day impairment/residual effect' and the efficacy measure 'next-day improvement'.

The sponsor notes that next-day residual effects were evaluated in all phases of the suvorexant clinical development programme, not just the Study P002 cited by the initial decision-maker as evidence of next-day impairment. With regard to P002, the sponsor contests the conclusion that there was any dose-response effect for Simple Reaction Time and Choice Reaction Time outcomes.

The sponsor proposes that the Phase III database may be more representative of the likelihood of effects than Phase I healthy subject studies.

The sponsor contests the initial decision-maker's interpretation of results of dedicated on-the-road driving studies (P035 and P039), while recognising that 'some individuals may be more sensitive to the residual effects of suvorexant on driving ability, and this risk can be managed through appropriate product labelling and appropriate pharmacovigilance'.

Suicidal ideation

The sponsor considers 'the small treatment imbalance [in suicidal ideation] is unlikely to represent a causal association with suvorexant' but recommends that patients and physicians should be cautioned of the possibility that suicidal ideation may emerge during treatment. The sponsor plans to address this risk through 'class labelling' and 'robust pharmacovigilance'.

Abnormal sleep behaviours

The sponsor clarifies that different abnormal sleep behaviours should trigger different degrees of concern. The sponsor notes the events' rarity, and that the frequency of these events at the starting dose is similar to frequency in the placebo arm. The sponsor argues that risk can be addressed via labelling and pharmacovigilance.

Demonstration of suvorexant efficacy

Duration of effect

The sponsor contends that improvements in sleep provided by suvorexant are sustained over time without evidence of tolerance.

The sponsor contends that 'improvement in next day effects' as being critical to demonstration of efficacy is not a standard that any sleep drug has been subjected to or met previously, and notes that it is not the primary endpoint for efficacy evaluations. The sponsor notes some endpoints did address this issue.

Magnitude of effect

The sponsor contests the initial decision-maker's view of the relevance of improvements to sleep that patients experienced in Phase III trials. The sponsor summarised data around: sleep onset; sleep maintenance; and patient and clinician -reported insomnia assessments, including Insomnia Severity Index outcomes.

Final outcome

The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's report.

Reasons for the Delegate of the Minister's decision

The Delegate of the Minister has been asked to reconsider whether suvorexant should be included on the ARTG. In order to reach a decision the Delegate of the Minister needs to form a view as to whether the quality, safety and efficacy of the goods for the purposes for

which they are to be used have been satisfactorily established. The Delegate of the Minister finds that in forming this view, the Delegate of the Minister needs to balance the evidence regarding safety and efficacy of suvorexant in the context of the purposes for which the good is to be used.

The Delegate of the Minister's decision about whether suvorexant should be included on the ARTG is recorded above. The section below explains the Delegate of the Minister's reasons for that decision.

The Delegate of the Minister acknowledges that untreated insomnia produces substantial morbidity for individuals and has major adverse impacts on the community at large. The Delegate of the Minister also acknowledges the unmet need for medical treatments that are safe and effective in long-term treatment of insomnia.

The Delegate of the Minister did not find any chemistry or manufacturing issues that would negatively influence my view of suvorexant's quality, safety, or efficacy.

The Delegate of the Minister finds that in balancing evidence regarding safety and efficacy of suvorexant in the context of the purposes for which it is to be used, the Delegate of the Minister needs to understand the *clinical significance* of the effect size demonstrated by suvorexant relative to placebo. The Delegate of the Minister notes the sponsor's implication that clinical significance is not an appropriate test under Section 25(1)(d) of the Act (Section 8.1.1 of the 'Appeal under Section 60') but the Delegate of the Minister considers that the evaluation of clinical significance is a key part of the assessment of a medicine's efficacy. Having said that, the Delegate of the Minister notes the importance of using an evidence-based approach to this aspect of evaluation. The Delegate of the Minister has attempted to adopt such an approach in this reconsideration.

The Delegate of the Minister considers that *main analyses* (that addressed differences between means) and certain *exploratory analyses* (that addressed the proportion of responders, that is, those attaining at least a minimal important difference) are both important approaches in determining clinical significance of efficacy outcomes.

The Delegate of the Minister estimates that the *efficacy* of suvorexant will reach (or exceed) a minimally important level in about 15 to 20 in 100 subjects with primary insomnia, after up-titration of dose where appropriate, after adjusting for the placebo response.

The fraction of primary insomnia subjects who experience serious/severe adverse reactions to suvorexant is low but *safety risks* will apply to all subjects using suvorexant, not just those who obtain relief from insomnia. Some adverse reactions may be more likely in responders, but the extent of this overlap is unclear. Some examples of safety concerns follow:

- Next-day drowsiness is a side-effect of suvorexant in at least 5 to 10% of people with primary insomnia, and may manifest as 'excessive day-time sleepiness'.
- Suvorexant impairs next-day driving in 'some' subjects, more so in non-elderly than elderly subjects, although the exact proportion is difficult to establish.
- With high doses there is a small increased risk of abnormal sleep behaviours, and also a small increased risk of suicidal ideation (which indicates to the review Delegate a risk in subjects with outlying pharmacokinetic or pharmacodynamic sensitivities at low doses).

The Delegate of the Minister is concerned that the incidence of important adverse events will *not* be reduced sufficiently by product labelling. The Delegate of the Minister's concern is shared by the TGA's Advisory Committee on Safety of Medicines. The committee '*could not detail any activities that could appropriately address concerns associated with real-world use*'.

- For example, it seems unlikely that CMI wording would much alter ingrained or necessary habits such as driving to work, dropping children off at school and so on, in many people over a prolonged period of time.
- The sponsor has argued that every important safety concern for suvorexant can be addressed sufficiently by product labelling. Even if the Product Information were extensively modified (for example, the Round 2 RMP evaluation), the Delegate of the Minister does not consider the practical impact of these changes would alter the product's efficacy/safety balance. The Delegate of the Minister cannot envisage feasible risk minimisation steps (including steps that go beyond PI / CMI changes, such as education campaigns) that *would* address the concerns the Delegate of the Minister has outlined about this balance.

The Delegate of the Minister concludes that suvorexant's safety profile in people with primary insomnia is not satisfactory for a product that provides tangible efficacy in approximately 15 to 20/100 subjects.

The Delegate of the Minister must consider suvorexant's profile in the treatment of insomnia, not just the treatment of primary insomnia. Safety and efficacy of suvorexant are only well-characterised in primary insomnia. There is no assurance that the same profile will apply to the 70 to 75% of patients with *co-morbid* insomnia. There is reason to suppose risks could be exaggerated in this large proportion of the population likely to use the product. It is unlikely practical measures could be put in place to restrict use to patients with primary insomnia.

Pharmacovigilance activities may measure (to some extent) the real-world safety of the product, but they do not reduce risk except in the sense that safety signals might lead to further risk minimisation steps. The Delegate of the Minister notes that only routine pharmacovigilance has been proposed to measure safety of suvorexant when it is marketed, except for a questionnaire for motor vehicle accidents and analysis of US Drug Abuse Warning Network data. The Round 2 RMP evaluator proposed additional pharmacovigilance activities, but the Delegate of the Minister does not consider these would directly address the efficacy/safety balance of the medicine.

The Delegate of the Minister does not consider it possible to identify *in advance* a subgroup of subjects with a favourable safety/efficacy balance. It is therefore not possible to limit approval to any 'subgroup most likely to benefit'.

Trial of therapy can in some settings identify subjects with a favourable safety/efficacy balance. The Delegate of the Minister does not think this approach would work here:

- There is a large placebo effect, so many subjects would improve for reasons not related to suvorexant (for example, impact of therapeutic context; the fluctuating nature of the condition).
- There is a moderate indication that suvorexant has abuse potential, which may if borne out in real-world drug utilisation result in ongoing use despite absence of 'benefit'.
- Most suvorexant safety issues are of immediate concern, that is, apply during any trial of therapy.

The Delegate of the Minister has considered if it is reasonable to register suvorexant on the basis that patients fully informed about the drug can make individualised decisions in consultation with their doctors about whether to use suvorexant or not. In the Delegate of the Minister's view this option is more appropriate in life-threatening/seriously debilitating illness and in the absence of alternative acceptable treatments.

- The Delegate of the Minister acknowledges that in some patients insomnia amounts to a debilitating illness and in some circumstances there are no other acceptable

treatments available. However, in others insomnia is less severe, or there are alternative treatments.

- Further, it is not possible to fully inform many patients about the drug's efficacy/safety balance because studies have only been performed in a minority of subjects (that is, those with primary insomnia). Comments made above about 'trial of therapy' also become relevant. Therefore, the Delegate of the Minister does not consider that registration of suvorexant on this basis is appropriate.

The Delegate of the Minister is also concerned that the sponsor recommends use of the lowest dose effective in a given subject but that there is a suggestion from the US FDA's evaluation process and decision that doses lower than recommended or even proposed for registration in Australia may have the best safety/efficacy profile. (There is insufficient information available to support registration here using the dose regimen approved in the USA.)

Delegate of the Minister's conclusion

For reasons referred to above, the Delegate of the Minister has found that the safety and efficacy of suvorexant for the purpose for which it is to be used has not been satisfactorily established and as such Delegate of the Minister decided to confirm the initial decision not to include suvorexant in the ARTG.

Result of the Delegate of the Minister's reconsideration of the initial decision

The Delegate of the Minister decided to confirm the initial decision under Section 60(3)(a) of the Act.

Appeal to the administrative appeals tribunal

Subject to the *Administrative Appeals Tribunal Act 1975*, the sponsor has at this stage made an application to the Administrative Appeals Tribunal (AAT) for a review of this decision. This AusPAR will be updated with the outcome of the AAT when known.

Attachment 1. Extract from the Clinical Evaluation Report

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