

**5.09 NALMEFENE,
oral tablets, 18mg,
Selincro[®], Lundbeck Australia P/L.**

1 Purpose of Application

1.1 The submission requested an Authority Required listing for nalmefene for the treatment of alcohol dependence.

2 Requested listing

2.1 The requested PBS listing is presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NALMEFENE Tablet, 18mg, 28	1	1	\$ [REDACTED]	Selincro [®] Lundbeck

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Alcohol dependence <i>use disorder with the goal of reduction in alcohol consumption</i>
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Patient must have undergone a psychosocial intervention during a pre-treatment baseline period of at least 2 weeks, but failed to achieve an adequate response. Patient must be treated in conjunction with a <i>undergoing concurrent</i> psychosocial intervention focused on treatment adherence and reduction of alcohol consumption.

Clinical criteria:	<p>Patient must be unable to reduce alcohol consumption to below an average of 6 standard drinks per day (for men) or 4 standard drinks per day (for women) <i>per day</i>;</p> <p>AND</p> <p>Patient must be without <i>not have</i> physical withdrawal syndrome;</p> <p>AND</p> <p>Patient must not require immediate detoxification or immediate abstinence;</p> <p>AND</p> <p><i>Patient must have undergone a psychosocial intervention during a pre-treatment baseline period of at least 2 weeks, but failed to achieve an adequate response.</i></p>
Population criteria:	Adult: Patient must be aged 18 years old or greater.
Administrative Advice	<i>This medicine is contraindicated in patients receiving opioid drugs.</i>

2.2 The ESC noted that the indication of alcohol dependence is consistent with the current indications for naltrexone and acamprosate, however, the TGA indication for nalmefene specifies “alcohol use disorder” consistent with the change in definitions between the DSM-IV and DMS-V, incorporating both alcohol abuse and alcohol dependence.

2.3 The basis for the requested listing was a cost-utility analysis compared with placebo (in combination with a psychosocial intervention); and a cost-minimisation analysis between nalmefene and naltrexone (in combination with a psychosocial intervention).

3 Background

3.1 TGA status at time of PBAC consideration: Nalmefene was TGA registered on 17 June 2015 for the reduction of alcohol consumption in adult patients with alcohol use disorder who have an average daily consumption of alcohol of >60g for men and >40g for women; only if the patient has failed to achieve an adequate response following psychosocial intervention for at least two weeks; in conjunction with continuing psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene is not suitable for patients with physical withdrawal syndrome or who require immediate detoxification.

3.2 Nalmefene has not been previously considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 The proposed algorithm suggested that nalmefene will provide an alternative treatment pathway for patients who do not require alcohol withdrawal management, when brief psychosocial intervention alone is not effective in reducing alcohol consumption. The submission suggested that patients unwilling or unable to comply with intensive abstinence based regimens including naltrexone, acamprosate or disulfiram in

combination with psychosocial intervention, would benefit from a controlled drinking regimen (reduction in alcohol consumption) based on nalmefene in combination with psychosocial intervention.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 Placebo plus supportive psychosocial intervention was nominated as the main comparator, with naltrexone nominated as a secondary comparator. The evaluation considered these were appropriate comparators. The submission acknowledged that naltrexone and acamprosate are currently listed on the PBS for the treatment of alcohol dependence, and that nalmefene is similar to naltrexone in class, structure and mechanism of action. However, the submission argued that the proposed place in therapy for nalmefene (reduction in alcohol consumption) is unique, and fills a clinical need not met by naltrexone or acamprosate (PBS listed for maintenance of abstinence). The evaluation noted that consideration should be given to whether naltrexone is an appropriate main comparator, given it is the nearest pharmacological analogue to nalmefene, it is similar in terms of mechanism of action and place in therapy and its TGA approved indication includes use in alcohol dependence generally, including reduction of consumption.
- 5.2 The PSCR (p1) maintained that naltrexone is an appropriate secondary comparator due to differences in treatment intent. The ESC considered that while naltrexone is currently PBS listed for the "goal of maintaining abstinence", it is likely that this is being used in practice as a method for reducing alcohol consumption. This was supported by a recent paper in the Australian Prescriber¹ which explicitly discussed the appropriate use of naltrexone as a therapy for reduced consumption of alcohol in addition to the goal of achieving abstinence. While the extent of such use is currently unknown, the ESC considered that a comparison with naltrexone would be the most informative to PBAC decision making. The pre-PBAC Response (p1) acknowledged that some specialists may advise some individual patients to use naltrexone when required (PRN) where they feel a goal of reduced drinking rather than abstinence was appropriate, but noted that such use was contrary to both the intent of the PBS restriction and the daily dosage regimen in the TGA approved Product Information.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

¹ Crowley P. (2015). Long-term drug treatment of patients with alcohol dependence. Australian Prescriber, 38(2) 41-43.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on three pivotal head-to-head randomised trials (SENSE, ESENSE 1 and ESENSE 2) comparing nalmefene 20mg as needed (PRN) to placebo (with both arms in combination with BRENDA psychosocial intervention). The submission relied on a pooled post-hoc subgroup analysis of patients with high to very high drinking risk levels at screening and randomisation from these three pivotal trials. Three supporting trials were also presented (CPH-101-0701, CPH-101-0801, CPH-101-0299) comparing various dose regimens of nalmefene to placebo (in combination with various motivational or psychosocial interventions intended to support a reduction in alcohol consumption or treatment compliance). Section B(i) of the submission presented an informal indirect comparison of nalmefene (SENSE, ESENSE 1, ESENSE 2, CPH-101-0701, CPH-101-0801, CPH-101-0299) versus naltrexone (Heinala 2001, Kranzler 2009, Sherwood Brown 2009, Anton 1999, Anton 2005 and Oslin 2015) using placebo in combination with various psychosocial interventions as a common comparator.

6.4 It should be noted that the clinical trials refer to the dose of nalmefene as 20mg (the quantity of nalmefene hydrochloride), rather than nalmefene 18mg (the quantity of nalmefene base).

6.5 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Nalmefene vs placebo (in combination with psychosocial intervention)		
SENSE (12013a)	A 52-week, randomised, double-blind, placebo-controlled, parallel-group, safety, tolerability, and efficacy study of nalmefene, as-needed use, in patients with alcohol dependence.	Date: 30 September 2011
	Van Den Brink, W et al: Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study.	<i>Journal of Psychopharmacology</i> (2014) 28(8):733-44.
ESENSE 1 (12014a)	Randomised, double-blind, placebo-controlled, parallel group, efficacy study of 20mg nalmefene, as-needed use, in patients with alcohol dependence.	Date: 28 September 2011
	Mann K, Bladstrom A, Torup L, Gual A, van den Brink W: Extending the treatment options in alcohol dependence: A randomized controlled study of as-needed nalmefene.	<i>Biol Psychiatry</i> (2013a) 73:706-713.
ESENSE 2 (12023a)	Randomised, double-blind, placebo-controlled, parallel group, efficacy study of 20mg nalmefene, as-needed use, in patients with alcohol dependence.	Date: 5 October 2011
	Gual A, He Y, Torup L, van den Brink W, Mann K: A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence.	<i>Eur Neuropsychopharmacol</i> (2013) 23:1432-1442
	Aubin, H. J., W. Van Den Brink, and P. Sorensen: ESENSE 2 - efficacy of nalmefene as-needed in alcohol dependent patients with high drinking risk levels.	<i>Alcohol and Alcoholism</i> (2013) 48:i47.
Supporting nalmefene vs placebo (in combination with psychosocial intervention)		

Trial ID	Protocol title/ Publication title	Publication citation
CPH-101-0701	Targeted CPH-101 in the treatment of heavy alcohol drinkers with impaired control. A randomised, double-blind, placebo-controlled study.	Date: 7 September 2004
CPH-101-0801	Targeted CPH-101 in the treatment of heavy alcohol drinkers with impaired control. A randomised, double-blind, placebo-controlled study with randomised withdrawal. 0-28 and 28-52 week evaluation.	Date: 29 October 2004
	Karhuvaara S, Simojoki K, Virta A, Rosberg M, Loyttyneimi E, Nurminen T, Kallio A, Makela R: Targeted nalmefene with simple medical management in the treatment of heavy drinkers: A randomized double-blind placebo-controlled multicenter study.	<i>Alcohol Clin Exp Res</i> (2007) 31:1179-1187.
CPH-101-0299	CPH-101 in heavy alcohol drinkers with impaired control. A 12 + 40 week placebo controlled dose response study. 52-week final report.	Date: 15 June 2006
	Anton RF, Pettinati H, Zweben A et al; A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence.	<i>J Clin Psychopharmacol</i> (2004) 24:421–428.
Naltrexone vs placebo (in combination with psychosocial intervention)		
Heinala 2001	Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair JD: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind, placebo-controlled trial.	<i>J Clin Psychopharmacol</i> (2001) 21:287-292.
Kranzler 2009	Kranzler HR, Tennen H, Armeli S, Chan G, Covault J, Arias A, Oncken C: Targeted naltrexone for problem drinkers.	<i>J Clin Psychopharmacol</i> (2009) 9:350-357.
	Kranzler HR, Armeli S, Covault J, Tennen H: Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment.	<i>Addict Biol</i> (2013) 8:193-201.
Sherwood Brown 2009	Brown ES, Carmody TJ, Schmitz JM, Caetano R, Adinoff B, Swann AC, Rush AJ: A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence.	<i>Alcohol Clin Exp Res</i> (2009) 3:1863-1869.
Anton 1999	Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK: Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial.	<i>Am J Psychiatry</i> (1999a) 156:1758-1764.
	Anton RF, Moak DH, Latham PK, Waid LR, Malcolm RJ, Dias JK, Roberts JS: Post treatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism.	<i>J Clin Psychopharmacol</i> (2001) 21:72-77.
Anton 2005	Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, Thevos A, Wang W, Woolson R: Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence.	<i>J Clin Psychopharmacol</i> (2005) 25:349-357.
Oslin 2015	Oslin DW, Leong SH, Lynch KG, Berrettini W, O'Brien CP, Gordon AJ et al. Naltrexone vs placebo for the treatment of alcohol dependence: A randomized clinical trial.	<i>JAMA Psychiatry</i> (2015) 72(5):430-437.

Source: Table 18, pp.84-86 and Table 53, pp.179-181 of the submission.

6.6 The key features of the randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	Design	N	Dose regimens	Risk of bias	Patient population	Outcomes	In modelled evaluation
Nalmefene vs placebo (in combination with psychosocial intervention)							
SENSE 52 weeks	R, DB, MC	675	Nalmefene 20mg PRN vs placebo	Low	Alcohol dependence (DSM-IV-TR),	Change from baseline in no. heavy drinking	Yes (post-hoc subgroup)

Trial	Design	N	Dose regimens	Risk of bias	Patient population	Outcomes	In modelled evaluation
ESENSE 1 24 weeks	R, DB, MC	604	Nalmefene 20mg PRN vs placebo	High	≥6 heavy drinking days/month	days/month and total alcohol consumption averaged over 28 days (g/day)	Yes (post- hoc subgroup)
ESENSE 2 24 weeks	R, DB, MC	740	Nalmefene 20mg PRN vs placebo	Low			Yes (post- hoc subgroup)
Supporting nalmefene vs placebo (in combination with psychosocial intervention)							
CPH-101- 0701 28 weeks	R, OL, MC	167	Nalmefene 10-40mg ^b PRN vs placebo	High	Difficulty controlling drinking, ≥18 heavy drinking days/month	Number heavy drinking days/month and mean change from baseline in total alcohol consumption averaged over 28 days (g/day)	N
CPH-101- 0801 28 weeks	R, DB, MC	403	Nalmefene 10-40mg ^b PRN vs placebo	Unclear			N
CPH-101- 0299 12 weeks	R, DB, MC	272	Nalmefene 5mg, 20mg or 40mg <u>once daily</u> vs placebo (PRN dosing 40 week extension)	Unclear	Alcohol dependence (DSM-IV-TR), ≥8 heavy drinking days/month		N
Naltrexone vs placebo (in combination with psychosocial intervention)							
Heinala 2001 32 weeks	R, DB, SC	121	Naltrexone 50mg once daily for 12 weeks then PRN for 20 weeks	Unclear	Alcohol dependence (DSM-IV), ≥5 standard drinks/day	Mean time to relapse to heavy drinking	N
Kranzler 2009 12 weeks	R, DB, SC stratified by dose regimen	163	Naltrexone 50mg PRN or daily vs matching placebo	Unclear	Alcohol dependence (DSM-IV), ≥24 (men) ≥18 (women) standard drinks/week	Mean number of standard drinks/day	N
Sherwood Brown 2009 12 weeks	R, DB, SC	50	Naltrexone 50mg daily vs placebo	Unclear	Bipolar disorder, alcohol dependence	Change in drinking days and heavy drinking days/week	N
Anton 1999 12 weeks	R, DB, SC	131	Naltrexone 50mg daily vs placebo	Unclear	Alcohol dependence (DSM-III-R), ≥5 standard drinks/day	Mean time to relapse to heavy drinking; proportion of days abstinent; mean drinks per drinking day	N
Anton 2005 12 weeks	R, DB, SC stratified by psycho- social intervene- tion	160	Naltrexone 50mg daily vs placebo	Unclear	Alcohol dependence (DSM-IV), ≥5 (men) ≥4 (women) standard drinks/day	Mean drinks per drinking day; proportion of days abstinent	N
Oslin 2015 12 weeks	R, DB, MC stratified by Asp40	221	Naltrexone 50mg daily vs placebo	Unclear	Alcohol dependence (DSM-IV),	Proportion drinking days and heavy drinking	N

Trial	Design	N	Dose regimens	Risk of bias	Patient population	Outcomes	In modelled evaluation
	allele				≥2 heavy drinking days/week, ≥21 standard drinks/week	days	

Source: Compiled during the evaluation.

Abbreviations: DB, double blind; DSM, Diagnostic and Statistical Manual of Mental Disorders; MC, multicentre; OL, open label; PRN, taken as required once daily on increased risk of heavy drinking; R, randomised; SC, single centre.

^a See definitions of HDD in Table 3 below.

^b Starting dose 20mg as needed, titrated to 10-40mg as required after 2 weeks.

^c Post-hoc subgroup comparison used in modelled evaluation

Table 3: Definitions of key drinking outcomes used in the randomised trials

	Standard drink (grams alcohol)	Heavy drinking days (HDDs)/month	Total alcohol consumption (TACg/day)
Nalmefene vs placebo (in combination with psychosocial intervention)			
SENSE, ESENSE 1 & ESENSE 2	Australian standard (converted) ^a : one standard drink = 10g	Women: ≥4 standard drinks or 40g/day Men: ≥6 standard drinks or 60g/day	Mean g/day averaged over 28 days
Supporting nalmefene vs placebo (in combination with psychosocial intervention)			
CPH-101-0701	UK standard: one standard drink = 8g	Women: ≥6 standard drinks or 48g/day Men: ≥8 standard drinks or 64g/day	Calculated from drinks/week averaged over 28 days
CPH-101-0801	Finland standard: one standard drink = 12g	Women: ≥4 standard drinks or 48g/day Men: ≥5 standard drinks or 60g/day	Calculated from drinks/week averaged over 28 days
CPH-101-0299	Defined in trial protocol: one standard drink = 12g	Women: ≥4 standard drinks or 48g/day Men: ≥5 standard drinks or 60g/day	Calculated from drinks/week averaged over 28 days
Naltrexone vs placebo (in combination with psychosocial intervention)			
Heinala 2001 32 weeks	Standard assumed one standard drink = 12g	≥5 standard drinks/day	Mean g/week averaged over 8 weeks
Kranzler 2009	US standard assumed one standard drink = 14g	Not reported	Calculated from mean drinks/day averaged over 2 weeks (estimated from graphic)
Sherwood Brown 2009	US standard assumed one standard drink = 14g	Not reported	Calculated from mean % change in drinks/drinking day
Anton 1999	US standard assumed one standard drink = 14g	Women: ≥4 standard drinks/day Men: ≥5 standard drinks/day	Calculated from mean drinks/drinking day averaged over 84 days
Anton 2005	US standard assumed one standard drink = 14g	Women: ≥4 standard drinks/day Men: ≥5 standard drinks/day	Calculated from mean drinks/drinking day averaged over 84 days
Oslin 2015	US standard assumed one standard drink = 14g	Women: ≥4 standard drinks/day Men: ≥5 standard drinks/day	Calculated from mean drinks/drinking day (estimated from graphic)

Source: Table 70, pp.264-265 of the submission.

^a Local definitions of standard drink used during investigation, converted to Australian national standard during analyses.

- 6.7 The ESC noted that patients with a range of mental health conditions including depression, anxiety and bipolar disorder were excluded from the trials. This was considered problematic as a significant proportion of patients presenting with alcohol use disorder may also have a mental health condition. The ESC therefore considered that the trial population may not be reflective of the likely PBS population.

Comparative effectiveness

- 6.8 The submission relied on a post-hoc subgroup analysis of the pivotal nalmefene trials, in the target population of patients with high or very high drinking risk levels at both screening and randomisation (i.e. 2 weeks after a psychosocial intervention). The ESC questioned the appropriateness of this psychosocial intervention given that the BRENDA intervention use in the trials is not a “stand-alone” non-pharmacological intervention designed to reduce alcohol consumption². It is rather an adjunctive intervention to increase medication compliance which may not be reflective of the types of psychosocial interventions delivered in routine practice. The ESC noted that a two week intervention duration is inconsistent with the one month criteria used in DSM. Furthermore, the ESC noted that such defined interventions tend not to be provided in routine care and there is good evidence that even with well-established interventions for disorders such as anxiety and depression, most routinely provided treatment does not meet the criteria for minimally adequate evidence-based treatment³.
- 6.9 The ESC noted that an ITT analysis was not performed in the pivotal trials. The submission used various forms of imputations including last observation carried forward (LOCF), baseline observation carried forward (BOCF) and placebo mean value. Given the limitations associated with these techniques, it was unclear why more advanced techniques such as multiple imputation were not considered.
- 6.10 In the pivotal nalmefene trials, heavy drinking days per month were defined as the number of days per month during which at least 4 standard drinks (40g) were consumed for women and at least 6 standard drinks (60g) were consumed for men.
- 6.11 Larger reductions in the number of heavy drinking days per month were reported in the post-hoc target subgroup analysis of patients with high to very high drinking risk levels at screening and randomisation treated with nalmefene compared to placebo over 24 weeks (3.02 fewer HDDs) and 52 weeks (2.7 fewer HDDs). However, patients at all other drinking risk levels (abstinent, low and moderate) showed no difference in the reduction of heavy drinking days per month compared to placebo at 24 weeks, but achieved larger reductions in the number of heavy drinking days per month compared to patients in the target population (Table 4). The ESC noted that for patients in abstinent, low and moderate drinking levels, significant reductions in HDDs were reported for both the placebo and nalmefene groups.

² Starosta, A. N., R. F. Leeman and J. R. Volpicelli (2006). "The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders." *J Psychiatr Pract* **12**(2): 80-89.

³ Heuzenroeder, L., M. Donnelly, M. M. Haby, C. Mihalopoulos, R. Rossell, R. Carter, G. Andrews and T. Vos (2004). "Cost-effectiveness of psychological and pharmacological interventions for generalized anxiety disorder and panic disorder." *The Australian And New Zealand Journal Of Psychiatry* **38**(8): 602-612.

Table 4: Change from baseline in number of heavy drinking days (HDDs) per month (*post-hoc* subgroup analyses; MMRM, FAS, OC)

Trial ID	Nalmefene ^a			Placebo ^a			Weighted mean difference (95 % CI) ^b
	n/N ^c	Baseline mean (SD)	Difference mean (SD)	n/N ^c	Baseline mean (SD)	Difference mean (SD)	
Target population at 24 weeks (high, very high baseline drinking risk level subgroup)							
SENSE	102/141	19.2 (6.25)	-7.1 (6.06)	32/42	18.6 (6.36)	-4.4 (5.66)	-2.70 (-4.99, -0.41)
ESENSE 1	85/171	23.0 (5.88)	-10.0 (7.38)	114/167	23.1 (5.46)	-6.1 (8.54)	-3.9 (-6.12, -1.68)
ESENSE 2	103/148	22.7 (5.92)	-10.7 (8.12)	111/155	21.6 (6.37)	-8.2 (7.37)	-2.4 (-4.58, -0.42)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =0%)						-3.02 (-4.28, -1.75)
Target population at 52 weeks							
SENSE	81/141	19.2 (6.25)	-9.7 (NR)	31/42	18.6 (6.36)	-5.8 (NR)	-3.9 (-6.0, -1.9)
Non-target population at 24 weeks (subgroup complement)							
SENSE	218/274	12.0 (4.89)	-10.7 (5.91)	78/95	12.0 (4.94)	-10.1 (6.18)	-0.2 (-1.6, 1.2)
ESENSE 1	67/119	14.5 (6.08)	-12.1 (7.37)	99/122	14.8 (5.91)	-11.8 (7.96)	-0.2 (-2.4, 2.0)
ESENSE 2	109/181	17.4 (6.84)	-14.5 (7.31)	118/171	15.7 (6.43)	-14.0 (7.60)	-0.5 (-2.4, 1.4)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =0%)						-0.27 (-1.36, 0.82)

Source: Table 98, pp.325-326; Table 95, pp.319-320; Figure 28, p.336 of the submission.

Abbreviations: CI, confidence interval; FAS, full analysis set; HDD, heavy drinking days; MMRM, Mixed model for repeat measures; OC, observed cases; SD, standard deviation;.

^a All therapies in combination with psychosocial intervention (BRENDA program).

^b Nalmefene – placebo, negative result favours nalmefene.

^c n/N refers to the number of patients contributing data at each time point by the baseline count of patients in that category. Note: Statistically significant results in bold.

- 6.12 In the *post-hoc* subgroup analysis, patients with high to very high drinking risk levels at screening and randomisation treated with nalmefene reported larger reductions in total alcohol consumption compared to placebo over 24 weeks. In the pooled comparison, the reduction was equivalent to approximately 1.5 Australian standard drinks per day averaged over 28 days, but overall mean total alcohol consumption remained high. Patients at all other drinking risk levels (non-target population) showed no difference in the reduction of total alcohol consumption between nalmefene and placebo, but reduced consumption to ≤1 Australian standard drink per day for both treatment and placebo arms (Table 5).

Table 5: Change from baseline in total alcohol consumption (TAC) in grams/day – (*post-hoc* subgroup analyses, MMRM, FAS, OC)

Trial ID	Nalmefene ^a			Placebo ^a			Weighted mean difference (95 % CI) ^b
	n/N ^c	Baseline mean (SD)	Difference mean (SD)	n/N ^c	Baseline mean (SD)	Difference mean (SD)	
Target population at 24 weeks (high, very high drinking baseline risk level subgroup)							
SENSE	102/141	100.7 (44.6)	-39.5 (28.3)	32/42	100.6 (46.9)	-23.8 (26.6)	-15.7 (-25.6, -5.8)
ESENSE 1	85/171	102.3 (42.9)	-46.4 (28.6)	114/167	98.6 (40.5)	-28.0 (31.0)	-18.5 (-26.0, -11.0)
ESENSE 2	103/148	113.9 (47.8)	-56.2 (32.5)	111/155	108.3 (47.9)	-46.2 (33.7)	-10.0 (-18.2, -1.9)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =0)						-14.8 (-20.1, -9.5)
Target population at 52 weeks							
SENSE	81/141	100.7 (44.6)	-47.6 (NR)	31/42	100.6 (46.9)	-31.8 (NR)	-15.8 (-26.1, -5.6)
Non-target population at 24 weeks (post-hoc subgroup complement)							
SENSE	218/274	55.9 (29.5)	-52.5 (29.5)	78/95	56.9 (31.5)	-54.0 (27.4)	1.5 (-5.0, 8.0)
ESENSE 1	67/119	59.6 (24.6)	-55.3 (29.5)	99/122	64.9 (34.6)	-54.7 (31.8)	-0.5 (-9.1, 8.1)
ESENSE 2	109/181	75.7 (38.8)	-68.2 (32.4)	118/171	72.7 (42.1)	-68.7 (33.7)	0.5 (-7.3, 8.2)

2							
Pooled results		SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =0)				-0.65 (-4.1, 5.4)	

Source: Tables 95 pp.319-320 and Table 99, p.328 of the submission.

Abbreviations: CI, confidence interval; FAS, full analysis set; MMRM, Mixed model for repeat measures; OC, observed cases; SD, standard deviation; TAC, total alcohol consumption.

^a All therapies in combination with psychosocial intervention (BRENDA program).

^b Nalmefene – placebo, negative result favours nalmefene.

^c n/N refers to the number of patients contributing data at each time point by the baseline count of patients in that category.

Note: Statistically significant results in bold.

- 6.13 Table 6 shows the proportions of patients achieving a reduction in drinking risk level from very high risk to at least moderate risk, or from high or medium risk to at least low risk. Results were not reported for the *post-hoc* subgroup. Between 67% and 78% of patients treated with nalmefene achieved a substantial reduction in drinking risk level at 24 weeks, but similarly high proportions were reported in patients taking placebo (57-76%). Only ESENSE 1 showed a statistically significant difference between nalmefene and placebo in terms of reduction in drinking risk level, but this difference may have been due to attrition bias in ESENSE 1 and failure to account for potential relapse in discontinuing patients in the nalmefene pivotal trials. Excluding ESENSE 1 from the analysis, there was no statistically significant difference in the proportions of patients achieving substantial reductions in drinking risk levels at 24 weeks or 52 weeks.

Table 6: Patients achieving a downward shift in drinking risk level – All patients (MMRM, FAS, LREG)

Trial ID	Nalmefene n/N ^a (%)	Placebo n/N ^a (%)	Odds ratio (95% CI)
All patients at 24 weeks			
SENSE	324/415 (78.07%)	104/137 (75.91%)	1.06 (0.64, 1.74)
ESENSE 1	203/290 (70.0%)	166/289 (57.4%)	1.71 (1.21, 2.44)
ESENSE 2	221/329 (67.17%)	206/326 (63.19%)	1.28 (0.89, 1.83)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =37%)		1.35 (1.03, 1.76)
	SENSE and ESENSE 2 (24 weeks; I ² =0%)		1.17 (0.90, 1.52)
All patients at 52 weeks			
SENSE	345/415 (83.13%)	103/137 (75.18%)	1.58 (0.94, 2.64)

Source: Table 39, p.152 and Table 40, p.153 of the submission; NMF vs PBO.rm5, Other, Electronic files to the submission.

Abbreviations: CI, confidence interval; FAS, full analysis set; MMRM, Mixed model for repeat measures; LREG, logistic regression.

^a n/N refers to the number of patients contributing data at each time point by the baseline count of patients in that category.

- 6.14 Table 7 shows the mean change in EQ-5D score in the pivotal nalmefene trials full analysis sets at 24 and 52 weeks. Results for the *post-hoc* subgroup analysis included in the economic model were not presented. There were improvements in EQ-5D VAS health state scores in both the nalmefene and placebo arms of the pivotal trials at 24 and 52 weeks. However, only ESENSE 2 showed a statistically significant difference between nalmefene and placebo. There were no statistically significant changes in EQ-5D utility index score in either the nalmefene or placebo arms of the pivotal trials.

Table 7: Mean change from baseline in EQ-5D at 24 weeks (ANCOVA, FAS, OC)

Trial ID	Nalmefene		Placebo		Weighted mean difference (95% CI)
	n/N ^a	Mean change (SE)	n/N ^a	Mean change (SE)	
Utility index (0-1) at 24 weeks					
SENSE	317/416	-0.0 (0.01)	106/136	-0.01 (0.02)	-0.01 (-0.05, 0.03)
ESENSE 1	155/289	0.02 (0.01)	211/289	0.01 (0.01)	0.01 (-0.02, 0.04)
ESENSE 2	207/262	0.05 (0.01)	228/266	0.02 (0.01)	0.03 (-0.01, 0.06)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =20%)				0.01 (-0.01, 0.03)
Utility index (0-1) at 52 weeks					
SENSE	262/NR	0.03 (NR)	98/NR	0.03 (NR)	0.0 (-0.04, 0.04)
VAS health state (0-100) at 24 weeks					
SENSE	314/412	3.14 (1.08)	103/135	1.93 (1.68)	1.21 (-2.31, 4.73)
ESENSE 1	154/283	4.69 (1.17)	208/284	3.41 (1.07)	1.28 (-1.51, 4.07)
ESENSE 2	200/254	6.67 (1.11)	221/260	3.51 (1.05)	3.17 (0.48, 5.85)
Pooled results	SENSE, ESENSE 1 and ESENSE 2 (24 weeks; I ² =0%)				2.25 (0.10, 4.39)
VAS health state (0-100) at 52 weeks					
SENSE	262/NR	8.76 (NR)	96/NR	7.0 (NR)	1.76 (-1.83, 5.35)

Source: Table 46, p.161 of the submission; NMF vs PBO.rm5, Other, Electronic files to the submission.

Abbreviations: ANCOVA, Analysis of covariance; EQ-5D, European Quality of Life- 5 Dimensions; FAS, full analysis set; NR, not reported; OC, observed cases; SE, standard error.

^a n/N refers to the number of patients contributing data at each time point by the baseline count of patients in that category.

- 6.15 The ESC noted that the results of the presented studies may not reflect the effects observed in clinical practice. The ESC considered that the real-world placebo response may be lower than in the trials as monthly follow up visits with a health care provider undertaken in the trials may not be adhered to in practice, noting that this is unable to be established from the data provided. However, it is also true that in real world practice, people taking nalmefene may not adhere to the routine follow-up visits. Therefore, the differential impact of this on comparative effectiveness is unknown.
- 6.16 The submission acknowledged limited exchangeability between the nalmefene and naltrexone trials due to fundamental differences in drinking outcomes, data analyses and reporting, but suggested an informal indirect comparison remained informative. The ESC noted the limitations identified in the exchangeability of the presented studies, and considered that a formal comparison between nalmefene and naltrexone might provide a more reliable basis for decision making. The pre-PBAC Response (p1) noted that there are no clinical trials which allow a direct comparison of nalmefene and naltrexone. Given the differences in trial design, the pre-PBAC Response considered that a formal indirect comparison was unfeasible, and that any formal indirect comparison would be no more informative than the informal comparison presented.

Table 8: Calculated outcomes for naltrexone trials (naltrexone vs placebo) at fixed time points

Trial	TAC (g/day)			HDD (days/month)			
	Naltrexone	Placebo	Difference	Naltrexone	Placebo	Difference	
Heinala 2001 (weeks 24-32)	Coping skills	33.0	50.6	-17.6	Not reported		
	CBT	51.0	46.6	4.4			
Kranzler 2009 (weeks 11-12)	PRN dosing, male	32.9	50.0	-17.1			
	female	41.4	38.9	2.5			
	Daily dosing, male	56.1	42.0	14.1			
	female	44.9	33.6	11.3			
Sherwood Brown 2009 (week 12)		22.0	45.9	-23.9	11.1	10.6	0.45

Trial	TAC (g/day)			HDD (days/month)		
	Naltrexone	Placebo	Difference	Naltrexone	Placebo	Difference
Anton 1999 (week 12) CBT	3.5	10.6	-7.1	Not reported		
Anton 2005 (week 12) CBT	3.9	11.5	-7.6			
MET	12.6	15.4	-2.8			
Oslin 2015 (week 12) Asp40+Asn40 pooled	13.7	21.5	-7.8			

Source: Table 81-90, pp.282-296 of the submission.

Abbreviations: Asn40, μ -opioid receptor gene homozygous for the Asn40 allele; Asp40, μ -opioid receptor gene Asp40 allele; CBT, cognitive behavioural therapy; HDD, heavy drinking days; MET, motivational enhancement therapy; TAC, total alcohol consumption.

Comparative harms

- 6.17 There were statistically significantly more nalmefene-treated patients reporting any adverse event compared to placebo. In terms of serious adverse events and adverse events leading to discontinuation, there were no statistically significant differences between treatment arms. There were two deaths reported in nalmefene treated patients and four deaths in placebo. No deaths were attributable to treatment with nalmefene.

Table 9: Summary of key adverse events in the randomised trials

Trial ID	Nalmefene n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	Risk difference (95% CI)	Relative risk (95% CI)
Any adverse events					
SENSE	386/509 (76%)	109/166 (66%)	1.64 (1.12, 2.40)	0.10 (0.02, 0.19)	1.15 (1.03, 1.31)
ESENSE 1	256/306 (84%)	207/298 (70%)	2.25 (1.52, 3.33)	0.14 (0.08, 0.21)	1.20 (1.10, 1.32)
ESENSE 2	248/358 (69%)	222/360 (62%)	1.40 (1.03, 1.91)	0.08 (0.01, 0.15)	1.12 (1.01, 1.25)
Serious adverse events					
SENSE	35/509 (7%)	9/166 (5%)	1.29 (0.61, 2.74)	0.02 (-0.04, 0.05)	1.27 (0.64, 2.56)
ESENSE 1	18/306 (6%)	20/298 (7%)	0.87 (0.45, 1.68)	-0.01 (-0.05, 0.03)	0.88 (0.48, 1.61)
ESENSE 2	8/358 (2%)	17/360 (5%)	0.46 (0.20, 1.08)	-0.03 (-0.06, 0.0)	0.47 (0.21, 1.06)
Adverse events leading to withdrawal					
SENSE	58/509 (11%)	5/166 (3%)	4.14 (1.63, 10.51)	0.08 (0.04, 0.12)	3.78 (1.61, 9.08)
ESENSE 1	70/306 (23%)	23/298 (8%)	3.55 (2.15, 5.86)	0.15 (0.10, 0.21)	2.96 (1.92, 4.62)
ESENSE 2	25/358 (7%)	26/360 (7%)	0.96 (0.55, 1.70)	-0.0 (-0.04, 0.04)	0.97 (0.57, 1.63)

Source: Figure 19, p.165 of the submission.

Note: Statistically significant results in bold.

- 6.18 The most common treatment emergent adverse events reported by patients treated with nalmefene in the key trials were nausea, vomiting, headache, dizziness and insomnia. Generally, nalmefene was well tolerated and adverse events were mild. The ESC considered that adverse events were likely to contribute to the high drop-out rate seen in trials.
- 6.19 The submission stated that nalmefene and naltrexone were similar in terms of safety, sharing several adverse events characteristic of opioid antagonists. Nalmefene, similar to naltrexone, is an opioid antagonist, and concurrent use with recreational or therapeutic opioids may result in precipitated opioid withdrawal, failure of therapeutic analgesia at usual therapeutic dose and the risk of inadvertent opioid overdose.

Benefits/harms

6.20 A summary of the comparative benefits and harms for nalmefene versus placebo is presented in the table below.

Table 10: Summary of comparative benefits and harms for nalmefene and placebo

Trial	Nalmefene			Placebo			Difference
Benefits							
Change from baseline in mean heavy drinking days (HDD)/month in target population							
	n	Mean Δ baseline HDD	SD	n	Mean Δ baseline HDD	SD	WMD (24 weeks) Nalmefene vs placebo (95% CI)
SENSE	102	-7.1	6.06	32	-4.4	5.66	-2.70 (-4.99, -0.41)
ESENSE 1	85	-10.0	7.38	114	-6.1	8.54	-3.9 (-6.12, -1.68)
ESENSE 2	103	-10.7	8.12	111	-8.2	7.37	-2.4 (-4.58, -0.42)
Pooled results* I ² =0%	290	NR	NR	257	NR	NR	-3.02 (-4.28, -1.75)
Change from baseline in total alcohol consumption grams/day (averaged over 28 days) in target population							
SENSE	102	-39.5	28.3	32	-23.8	26.6	-15.7 (-25.6, -5.8)
ESENSE 1	85	-46.4	28.6	114	-28.0	31.0	-18.5 (-26.0, -11.0)
ESENSE 2	103	-56.2	32.5	111	-46.2	33.7	-10.0 (-18.2, -1.9)
Pooled results* I ² =0%	290	NR	NR	257	NR	NR	-14.8 (-20.1, -9.5)
Harms							
	Nalmefene	Placebo	RR (95% CI)	Event rate/100 patients #		RD (95% CI)	
				Nalmefene	Placebo		
Nausea							
SENSE	112/509	9/166	NR	22	6	0.17 (NR)	
ESENSE 1	83/306	18/298	NR	28	6	0.21 (NR)	
ESENSE 2	58/358	20/360	NR	17	6	0.11 (NR)	
Insomnia							
SENSE	74/509	11/166	NR	15	7	0.08 (NR)	
ESENSE 1	30/306	10/298	NR	10	3	0.06 (NR)	
ESENSE 2	49/358	22/360	NR	14	7	0.08 (NR)	
Dizziness							
SENSE	73/509	6/166	NR	15	4	0.11 (NR)	
ESENSE 1	83/306	23/298	NR	28	8	0.19 (NR)	
ESENSE 2	52/358	15/360	NR	15	5	0.10 (NR)	

* Pooled results are from key trials SENSE, ESENSE 1 and ESENSE 2. Individual trial results are presented in Tables B.6.2 and B.6.5 of the commentary.

Trial durations were as follows: SENSE, 52 weeks; ESENSE 1 and ESENSE 2, 24 weeks.

Abbreviations: CI, confidence intervals; HDD, heavy drinking day; SD, standard deviation; WMD, weighted mean difference

Source: Compiled during the evaluation

6.21 On the basis of direct evidence presented by the submission, the comparison of nalmefene and placebo resulted in:

- A reduction of approximately three heavy drinking days per month over 24 weeks of therapy, in the target population of patients with high to very high drinking levels. The submission did not indicate what difference in heavy drinking days was considered to be clinically meaningful. The ESC considered that any reduction in

heavy drinking days has the potential to be clinically meaningful given the associated high risk behavior likely to be exhibited by people on heavy drinking days.

- A reduction of approximately 14.8 grams of alcohol consumed per day (averaged over 28 days) over 24 weeks of therapy, in the target population of patients with high to very high drinking levels. This reduction is equivalent to approximately 1.5 Australian standard drinks per day. The submission did not indicate what difference in total alcohol consumption was considered to be clinically meaningful.
- For every 100 patients treated, patients treated with nalmefene compared to placebo would experience (over 24 to 52 weeks):
 - Between 11 and 24 additional nausea adverse events
 - Between 6 and 17 additional insomnia adverse events
 - Between 8 and 19 additional dizziness adverse events.

Clinical claim

6.22 The submission described nalmefene as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo (in combination with a psychosocial intervention). This claim was adequately supported in terms of safety, but poorly supported in terms of efficacy for the overall population (full analysis set) and only partially supported in the target population (i.e. patients with high drinking levels):

- The clinical benefits of taking nalmefene were small and represented a further reduction of only three fewer heavy drinking days per month and 1.5 fewer Australian standard drinks per day compared to placebo in the post-hoc subgroup analysis of patients with high or very high drinking levels.
- Substantial reductions in heavy drinking days per month and total alcohol consumption were achieved by some patients using psychosocial interventions alone.
- Similar proportions of patients in both the nalmefene and placebo arms of the pivotal trials achieved a downward shift in drinking risk level from very high risk to at least moderate risk, or from high or moderate risk to at least low risk levels.

6.23 The submission described nalmefene as non-inferior in terms of comparative effectiveness and safety compared to naltrexone (in combination with a psychosocial intervention). This claim was not adequately supported. The nalmefene and naltrexone trials presented in the submission were not comparable due to differences in trial design, population, dose regimens, outcomes and severity of alcohol dependence. Outcomes included in the informal indirect comparison for the naltrexone trials were derived from other outcomes using one or more assumptions around standard drink alcohol content and definitions of heavy drinking days and were not reliable. The ESC considered that the claim that nalmefene was non-inferior to naltrexone in the treatment of alcohol dependence was not well supported, given the issues with the reliability of the informal comparison. The ESC noted that given naltrexone is the most appropriate main comparator, a formal comparison may be appropriate to give a more reliable estimate of the comparative efficacy and basis for decision making.

- 6.24 The PBAC considered that the claim of superior comparative effectiveness over placebo was reasonable, however considered that the clinical relevance of this was unknown.
- 6.25 The PBAC considered that the claim of inferior comparative safety over placebo was reasonable.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness and safety compared to naltrexone was unable to be determined from the data presented.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.27 The submission presented two economic evaluations:
- a modelled economic evaluation based on the results of the post-hoc subgroup analysis of patients with high to very high drinking levels from the pivotal placebo-controlled nalmefene trials; and
 - a cost-minimisation analysis of nalmefene versus naltrexone based on the submission’s informal indirect analysis.
- 6.28 The results of the two economic evaluations were combined to justify the price for nalmefene, with the proposed price a weighted average of the two prices, assuming one-third of patients treated with nalmefene would otherwise receive naltrexone. No justification was provided for this assumption. Given the large difference in price for nalmefene depending on comparator, this has a substantial impact on the weighted price of nalmefene. The ESC agreed that the proposed weighting was not adequately supported.

Table 11: Weighted average price proposed for nalmefene

Comparator	Proposed price (DPMQ)	Justification	Weighting
Placebo	\$ [REDACTED]	Incremental cost per QALY of approximately \$ [REDACTED]	67%
Naltrexone	\$ [REDACTED]	Cost-minimisation analysis based on one to one equi-effective dosing	33%
All	\$ [REDACTED]	Weighted average price across comparators	100%

Source: Table 120, p367 of the submission

^a Proposed DPMQ corrected for August 2015 price of naltrexone, calculated on AEMP.

- 6.29 A summary of the structure and rationale of the modelled economic analysis comparing naltrexone and placebo is presented in the table below.

Table 12: Summary of model structure and rationale

Methods used to generate results	Markov cohort expected value analysis with half-cycle correction
Time horizon	5 years
Cycle length	Monthly
Treatments	Nalmefene plus psychosocial intervention vs psychosocial intervention alone (placebo)
Health states	- five nalmefene drinking level health states (very high, high, medium, low and abstinence); - five placebo drinking level health states;

	<ul style="list-style-type: none"> - two 'discontinued all treatments' states (can only enter in the first year; at high and very high drinking levels): <ul style="list-style-type: none"> o utilities from these health states were sourced from the EQ5D collected in the trials. The ESC noted that SF-36 was also collected in all trials and considered that SF-6D utilities derived from the SF-36 would be an informative sensitivity analysis. - five alcohol-related chronic disease states (ischaemic heart disease; ischaemic stroke; haemorrhagic stroke; liver cirrhosis; and pancreatitis). The ESC considered that these are likely to be overestimates of the health loss associated with these states. - three dead states (death from alcohol-related chronic disease; death from alcohol-related injury; and death from non-alcohol causes).
Outcomes	Total alcohol consumption; quality-adjusted life years
Transition probabilities	Short term drinking risk transitions; long term drinking risk transitions; and alcohol-related injury, death and disease transitions; and all-cause mortality.
Discount rate	5% for costs and outcomes
Software package	TreeAge 2009

Source: compiled during the evaluation

- 6.30 Nalmefene drug costs, utility differences between drinking states, and the time horizon used were key drivers of the model and favoured nalmefene, as shown in Table 13 below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Nalmefene drug costs	Weighted price based on assumed proportion of substitution from naltrexone (33%).	High, favours nalmefene
Utility differences between drinking states	Different utilities for five drinking level health states; significant overlap between estimates; unclear whether differences represent meaningful differences in utilities.	High, favours nalmefene
Time horizon	Base case 5 years; transition probabilities beyond first 6 months unreliable.	High, favours nalmefene

Source: compiled during the evaluation

- 6.31 The transition probabilities between drinking level states in the first year of the model were based on individual patient data from the post-hoc subgroup of the pivotal nalmefene trials. Data to populate the transition probabilities between the five drinking levels (very high, high, medium, low and abstinent) and discontinuation states were sparse beyond six months. There was a disconnect between data at the end of month 6 and the beginning of month 7 – due to no data being available beyond 6 months for the 24-week ESENSE 1 and ESENSE 2 trials and only data from the 52-week SENSE trial being available. As a result, transition probabilities from later time points (i.e. beyond six months) may not be reliable.
- 6.32 In years 2-5 of the model, a number of assumptions were made regarding allowed transitions that were not adequately justified and may not reflect clinical practice:
- patients in the medium drinking level state are unable to transition to the abstinent state;
 - patients in the abstinent or low drinking level states can relapse to high or very high drinking levels, but not medium drinking levels; and
 - patients in the high and very high drinking levels are unable to move to any lower drinking level state.

- 6.33 The model does not allow patients to re-trial nalmefene or initiate other treatments for alcohol dependence, such as naltrexone or acamprosate, which may not reflect clinical practice.
- 6.34 The ESC noted that the PSCR (p3) incorrectly claimed the economic model permits retreatment of relapsing patients. While the published economic model (on which the submission's model was based) included retreatment of relapsing patients, the model presented in the submission did not allow retreatment. The pre-PBAC Response (p2) acknowledged this error. The PSCR also claimed the economic model included yearly cycles in years 2 to 5, had three drinking risk level health states and included treatment with naltrexone or acamprosate for non-responders. The submission's model had monthly cycles in years 2-5, five drinking risk level states and did not allow treatment with naltrexone or acamprosate.
- 6.35 The ESC noted that the model used traditional methods to convert yearly risks of adverse events to monthly rates. The ESC noted that alternative methods, such as the eigendecomposition approach⁴, may be superior. The ESC noted that it is unclear what impact this will have on the ICER.
- 6.36 The ESC considered that utilities for alcohol related serious events are likely to be overestimated. These utilities, which were derived during acute phase of illness, were applied for the duration of the model despite not being appropriate beyond acute phases. Furthermore, the ESC noted that the impact of these events on subsequent drinking patterns was not included in the model. This appeared clinically unlikely as people with a serious health risk may be more likely to reduce their alcohol consumption. The impact of this is unclear.
- 6.37 The model assumed that patients at abstinent or low and high or very high drinking levels after 12 months cease nalmefene treatment. This assumption was inadequately justified as patients may continue nalmefene treatment if it is considered to offer some benefit. The ESC considered that this was unlikely to be clinically plausible given the chronic episodic nature of the condition, and noted that data from the low risk and abstinent group at baseline from all trials suggests that such people do continue to use medications despite treatment success.
- 6.38 The ESC noted that some of the costs utilised in the model may not be appropriate, in particular:
- Costs associated with psychosocial interventions. The cost of social workers was used in the model which attracts a lower MBS cost compared to psychologists. Variations around these estimates should be assessed in a sensitivity analysis;
 - Incident-based costs associated with ischaemic heart disease and stroke should not have been used as patients may not be experiencing their first event;
 - Ongoing treatment costs outside of hospitalisation were not used for other serious events (pancreatitis, cirrhosis and injury).
- 6.39 No justification was provided for the five-year time horizon in the submission. Although a longer time horizon allows the impact of alcohol related events and deaths to be

⁴ Chhatwal, J., Jayasuriya, S., Elbasha, E (2014), Changing Cycle Lengths in State-Transition Models: Doing it the Right Way. ISPOR Connections, 20 (5)

included, these events only had a moderate impact on the economic model. The model was largely driven by the time spent in drinking level states. There was considerable uncertainty associated with transition probabilities between drinking level states beyond six months and transitions between states in years 2-5 were considered unreliable and optimistic.

- 6.40 The model assumed an instantaneous reduction in risk of alcohol related serious events and deaths from these events is associated with changing drinking level, which ignores accrued damage from drinking at high levels and was considered implausible. However this assumption was tested in a sensitivity analysis and had only a moderate impact on the economic model.
- 6.41 The key drivers of the model were nalmefene drug costs, the utility differences between the various drinking level health states and the time horizon of the model.
- 6.42 The results of the base case economic evaluation are presented in the table below. These values have been corrected for errors in discounting.

Table 14: Results of the modelled economic evaluation

Component	Nalmefene	Placebo	Increment
Costs	\$ [REDACTED]	\$4,099	\$ [REDACTED]
QALYs	3.6407	3.6029	0.0378
Incremental cost/QALY gained			\$ [REDACTED]

Source: Constructed during the evaluation using NALmodel_JULY2015 TreeAge model provided with the submission

- 6.43 The ICER should not be considered reliable due to concerns about transition probabilities beyond the first six months of the trials, utilities and costs. The model was sensitive to the time horizon of the model, with an ICER of \$105,000/QALY – \$200,000/QALY when the time horizon is one year.
- 6.44 For the cost-minimisation analysis against naltrexone, the equi-effective doses were estimated as nalmefene 20mg and naltrexone 50mg, based on the recommended maximum daily dose of each agent. In addition, the submission argued that differences in dose regimens between nalmefene (as required dosing) and naltrexone (daily dosing) required the calculation of nalmefene dose intensity (average dose over 28 days) to ensure comparability between regimens. However, the submission ultimately proposed a conservative approach due to uncertainties in the derivation of dose intensities, and assumed a dose ratio of 1:1 between the two therapies. Given the non-inferiority of nalmefene to naltrexone was not adequately demonstrated in the clinical trials, the cost minimisation analysis was not appropriate and the equi-effective doses were assumed. The ESC considered that while non-inferiority between nalmefene and naltrexone was not well supported by the informal indirect comparison presented, if this clinical claim is accepted then a formal cost minimisation analysis against naltrexone would be appropriate.
- 6.45 Results of the cost-minimisation analysis are presented in Table 15.

Table 15: Cost minimisation analysis

	DPMQ	AEMP	Maximum quantity	AEMP/tablet
Naltrexone	\$127.92	\$109.28	30 tablets	\$3.64
Nalmefene	\$ [REDACTED] ^a	\$ [REDACTED]	28 tablets	\$ [REDACTED]

	DPMQ	AEMP	Maximum quantity	AEMP/tablet
(proposed)				

Source: EXCEL spreadsheet "NMF_CostMin_JULY2015" to the submission.

^a Includes wholesale mark-up of 7.52%, AHI \$3.49 and dispensing fee \$6.76.

Note: The submission presented the cost minimisation based on DPMQ adjusted for maximum quantities, using June 2015 price information. The analysis was recalculated during the evaluation using the August 2015 listed price for naltrexone, and adjusting AEMP for differences in maximum quantities.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/year: \$ [REDACTED].

6.46 The estimated cost of nalmefene assumed 7.33 nalmefene scripts/patient/year (adjusted for dosing as required (PRN) and pack size). The comparative cost of naltrexone was \$ [REDACTED] assuming 9.48 scripts/patient/year (adjusted for compliance and pack size).

Estimated PBS usage & financial implications

6.47 This submission was considered by the Drug Utilisation Sub-Committee (DUSC). The submission used a mixed epidemiological and market share approach to estimate the extent of use and financial implications of listing nalmefene.

6.48 The net cost of listing nalmefene on the PBS was estimated by the submission to be up to \$10 – \$20 million in the fifth year of listing, including all cost offsets proposed. The evaluation considered the estimated utilisation and financial implications of listing nalmefene on the PBS were highly uncertain due to the following issues:

- Nalmefene may be used outside the requested restriction, in the broader population of patients with alcohol related disorders. The estimated number of patients likely to initiate treatment with nalmefene may be underestimated;
- The proportion of patients with alcohol dependence seeking treatment (22.4%) was based on the number of patients reporting "any alcohol use disorder" (alcohol dependence and alcohol abuse), using health services for "mental health problems". This does not reflect the proposed eligible population in terms of diagnosis, severity of alcohol dependence or failure of prior psychosocial intervention alone. The impact of this unclear;
- The assumption that 33% of patients initiating treatment with nalmefene prior to detoxification or withdrawal management, would switch from naltrexone was not supported. However, DUSC agreed that substitution may occur in practice;
- Patients successfully reducing alcohol consumption using nalmefene would be likely to continue to use nalmefene after detoxification and withdrawal management, and substitute for naltrexone outside the nalmefene requested restriction as an additional utilisation not accounted for in the estimates;
- The costs of psychosocial interventions associated with substituted naltrexone treatment are cost neutral and should not be treated as a cost savings. DUSC agreed that these should not be treated as cost savings;
- The use of naltrexone utilisation (10% Medicare sample) to estimate the 'time-in-treatment' for nalmefene was not appropriate;
- Cost savings to government from avoidance of alcohol-related injuries and chronic

health events derived from the economic model included hospital, non-hospital and patient out of pocket expenses, were overestimated and unlikely to be fully realised in clinical practice.

6.49 Additionally, DUSC considered:

- that uptake would be influenced by willingness to trial by individuals with alcohol dependence and how practitioners perceive the place in therapy. Furthermore, DUSC noted that therapies for alcohol abstinence or reduction may be prone to fluctuations;
- patients using naltrexone on an “as needed” basis are more likely to consider using nalmefene than naltrexone patients on a daily dosing regimen. Therefore, DUSC suggested the substitution ratio would more likely be 1:1 than the sponsor’s estimated 1:1.3 and considered the cost offsets attributed to naltrexone substitution would not be realised in practice;
- that the use of naltrexone utilisation (10% Medicare sample) to estimate the ‘time-in-treatment’ for nalmefene was not appropriate.

Table 16: Estimated cost to the PBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
% people w/ alcohol dependence who want treatment	10%	18%	25%	33%	40%
Number of patients initiating nalmefene	█	█	█	█	█
Total patient years of therapy (initiating + continuing patients) ^a	█	█	█	█	█
Scripts ^b	█	█	█	█	█
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$818,531	\$1,462,844	\$2,119,026	\$2,787,680	\$3,467,120
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█

The redacted table above shows that the number of patients initiating with nalmefene is estimated to be less than 10,000 in Year 1 and 10,000 – 50,000 in Year 5. The estimated net cost to the PBS is less than \$10 million in Year 1 and \$10 - \$20 million in Year 5.

Quality Use of Medicines

6.50 The sponsor identified that variability in psychosocial support and the quality of prescribing could impact on health outcomes for patients receiving nalmefene treatment. Hence the sponsor proposed an online self-help program for patients and an online continuing education program for general practitioners. Multiple online resources and programs for alcohol dependence are currently available to patients and health practitioners at no cost.

6.51 DUSC noted that the BRENDA psychosocial intervention was specifically developed for use with nalmefene, and that this may not be reflective of standard practice in the

Australian clinical context. DUSC considered that the absence of a definition of “psychosocial intervention” in the restriction may affect the variety and quality of therapy accessible by nalmefene patients, as well as the effectiveness of nalmefene use.

- 6.52 DUSC questioned the evidence base underpinning the two week trial period of psychosocial therapy, noting a two week period of psychosocial intervention is unlikely to be sufficient to achieve a clinically meaningful response.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Financial Management – Risk Sharing Arrangements

- 6.53 The sponsor indicated willingness to negotiate a risk share arrangement, and proposed an aggregate spending cap that would manage the risk of utilisation of nalmefene outside the proposed PBS restrictions and address the potential for higher than expected substitution rates of naltrexone.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of nalmefene for the treatment of alcohol dependence. In reaching this conclusion, the PBAC considered that the clinical place of therapy was not well defined and therefore the comparator was uncertain. The PBAC also considered that it was not clear whether the demonstrated effect was clinically meaningful. Without clarity around these issues, the clinical effectiveness of nalmefene in the proposed population could not be determined.
- 7.2 The PBAC considered that the clinical place in therapy was unclear and considered that consultation with hepatologists and addiction specialists may assist in determining the most appropriate clinical place for nalmefene.
- 7.3 Given the lack of clarity around the place in therapy, the PBAC considered that it was difficult to determine the appropriate comparator. The PBAC agreed with the ESC that naltrexone might be an appropriate comparator, but noted that the differences in outcomes between the naltrexone and nalmefene trials meant that any comparison between the two was unlikely to give a reliable estimate of their comparative efficacy.
- 7.4 Based on the results of the studies presented, PBAC agreed with the clinical claim that nalmefene is an effective intervention for the reduction of heavy drinking days compared to placebo in the target population of patients with high to very high drinking levels. However; it was unclear whether the results were clinically meaningful, and the value of the health outcomes, particularly in relation to the long term health effects of reduced alcohol consumption, remained unknown. The PBAC noted that the results of the studies presented may not be applicable to the PBS population due to the exclusion criteria of the studies, and because the psychosocial intervention in the study may not align with current clinical practice.
- 7.5 Given the differences between nalmefene and naltrexone, both in terms of treatment goals and the data available in the studies, the PBAC considered that comparative

effectiveness of nalmefene to naltrexone was difficult to assess, and the claim of non-inferiority was not well supported. The PBAC considered that given the similar mechanism of action, the claim of non-inferior comparative harms of nalmefene compared to naltrexone was reasonable.

- 7.6 The PBAC noted the advice from ESC that a formal comparison between nalmefene and naltrexone might provide a more reliable basis for decision making. However; the PBAC agreed with the Pre-PBAC Response that the differences between the studies for each product meant that such a comparison would be difficult and any result was unlikely to give a more reliable estimate of comparative efficacy than the informal comparison presented.
- 7.7 The PBAC agreed with the ESC that the economic analysis did not give an adequate basis for justification of the requested price. The PBAC noted the issues raised by the ESC in terms of the economic model, including:
- transition probabilities after 6 months being unreliable
 - assumptions regarding allowed transitions between health states in years 2-5 were not well justified and were unlikely to represent clinical practice
 - the model did not allow patients to re-trial nalmefene or initiate other treatments
 - the model did not include all appropriate costs
- 7.8 The PBAC considered that the five year time horizon of the model was appropriate, and noted that any additional longer term benefits of treatment would not be captured.
- 7.9 The PBAC accepted the advice of the DUSC, noting that the estimates of utilisation were uncertain given that the place in therapy was unclear. The PBAC agree that there would be some substitution for naltrexone, however the assumption of 33% from the submission was not supported by evidence. Overall, the PBAC considered that the cost-offsets for naltrexone were not likely to be realised in practice, and that nalmefene should not be priced greater than naltrexone.
- 7.10 Given the lack of clarity around the place in therapy for nalmefene and the clinical value of the health benefits observed in the evidence, the PBAC recommended a stakeholder meeting be held between the Department and relevant professionals.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Lundbeck Australia is disappointed with the PBAC's decision as we believe there is a clear clinical role for Selincro and that new treatment options are needed to address alcohol-related harm in Australia.