

**5.02 BUPRENORPHINE, Injection,
 8 mg in 0.16 mL pre-filled syringe,
 16 mg in 0.32 mL pre-filled syringe,
 24 mg in 0.48 mL pre-filled syringe,
 32 mg in 0.64 mL pre-filled syringe,
 64 mg in 0.18 mL pre-filled syringe,
 96 mg in 0.27 mL pre-filled syringe,
 128 mg in 0.36 mL pre-filled syringe,
 Buvidal®, Camurus AB.**

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Opiate Dependence Treatment Program) or a Section 85 listing for prolonged release subcutaneous injection of buprenorphine for the treatment of opioid dependence. Prolonged release buprenorphine has not been previously considered by the PBAC.
- 1.2 Listing was requested on a cost-effectiveness basis compared with sublingual buprenorphine/naloxone.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with opioid dependence
Intervention	Prolonged-release once weekly or once monthly subcutaneous injection of buprenorphine
Comparator	Sublingual buprenorphine/naloxone RBP-6000 (an alternative subcutaneous depot preparation of buprenorphine) identified as a potential near market comparator
Outcomes	Responder rate (based on predefined proportions of negative urine toxicology or self-report of illicit opioid use for the duration of the study), percentage of urine samples negative for illicit opioids, cumulative distribution function of percent samples that were negative for illicit opioids (Week 5-25) (supported by self-reported illicit opioid use), time to sustained abstinence of opioid use, trial retention rate, quality of life (Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH); EQ-5D-5L Health Questionnaire), adverse events
Clinical claim	In patients with opioid dependence, prolonged release buprenorphine is more effective than sublingual buprenorphine/naloxone at increasing the mean percentage of negative urine samples supported by self-reports of illicit opioid use, and comparable in terms of safety No clinical claim was made regarding the comparison with RBP-6000, due to poor exchangeability of trials

Source: Table 11, p.2 of the submission.

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Ex-manufacturer price	Proprietary name and manufacturer
BUPRENORPHINE 50 mg/mL weekly subcutaneous depot injection, pre-filled syringe				
8 mg in 0.16 mL	1	NA	\$ [REDACTED]	BUVIDAL WEEKLY Camurus AB
16 mg in 0.32 mL	1	NA	\$ [REDACTED]	
24 mg in 0.48 mL	1	NA	\$ [REDACTED]	
32 mg in 0.64 mL	1	NA	\$ [REDACTED]	
BUPRENORPHINE 356 mg/mL monthly subcutaneous depot injection, prefilled syringe				
64 mg in 0.18 mL	1	NA	\$ [REDACTED]	BUVIDAL MONTHLY Camurus AB
96 mg in 0.27 mL	1	NA	\$ [REDACTED]	
128 mg in 0.36 mL	1	NA	\$ [REDACTED]	

Category/Program:	Section 100 Opiate Dependence (or Section 85)
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
Condition:	Opiate dependence
PBS Indication:	Opiate dependence
Clinical criteria:	The treatment must be within a framework of medical, social and psychological treatment. AND The treatment must be administered by a health care professional
Notes	Care must be taken to comply with the provisions of State/Territory law when prescribing and administering this drug. Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners

- 2.1 The submission provided pricing information at the ex-manufacturer level, which may be appropriate if a decision is made for prolonged release buprenorphine to be a Section 100 (Opiate Dependence) listing. Under the current Opiate Dependence Treatment Program (ODTP) arrangements, the Commonwealth funds the full cost of the medicines via direct payments to the drug sponsors. Sponsors organise delivery of the product to dispensing sites, which can be hospital and community pharmacies, alcohol and drug treatment clinics or other public or private health clinics. Currently, all treatments subsidised under the ODTP restrict supply to clinics and pharmacies that are approved by State and Territory governments and prices are listed at the ex-manufacturer level.
- 2.2 Each state and territory operates individual programs for access to opiate substitution therapy (OST). Under these arrangements, jurisdictions approve prescribers, patients and dosing sites for participation in the program. In some jurisdictions, participation numbers for patients, prescribers and dosing sites can be capped. Due to potential capping of patient numbers, the increase system capacity claimed in the submission

may not be realised in practice. Prescribers of OST medicines must seek authority approval from their state health department.

- 2.3 The requirement for prolonged release buprenorphine administration by a GP or nurse eliminates the requirement for pharmacists to supervise dose administration at community pharmacies, and therefore the submission argued that restricting supply of prolonged release buprenorphine to approved pharmacies only may not be necessary. The submission stated that this may therefore warrant consideration of a General Schedule (Section 85) listing for prolonged release buprenorphine, provided appropriate contingencies could be built in to ensure fulfilment of local legislative requirements regarding Schedule 8 drugs and non-possession by the patient.
- 2.4 General Schedule listing of prolonged release buprenorphine is unlikely to be implementable. The submission suggested that, as patients cannot personally handle the product, the medicine would be delivered directly to the prescribers' rooms instead of the pharmacy. In this proposed scenario, the prescriber would facilitate a prescription to the pharmacy for claiming. As the medicine would never have physically been at the pharmacy premises to facilitate the supply and PBS claim, this would be a breach of the conditions of approval of the Section 90 (community) pharmacy. The ESC further considered that a General Schedule listing was problematic as it would preclude some incarcerated people from accessing this treatment. Given the potential advantages of administering a monthly injectable opioid substitution product for prisoners, the ESC considered that it was more appropriate for a listing to occur under Section 100.
- 2.5 The proposed Section 100 listing is consistent with existing Section 100 (Opiate Dependence) listings, except for the requirement that a health care professional administer prolonged release buprenorphine.
- 2.6 Currently access to products under Section 100 (Opiate Dependence) is primarily provided through community pharmacies, representing an estimated 75% of patients. Listing prolonged release buprenorphine will be a significant shift away from this model, as the product will be administered directly by a health professional (medical practitioner or nurse practitioner). The Pre-Sub-Committee Response (PSCR) maintained it was not within the scope of the submission to determine how the practice model should work, but proposed that pharmacists could arrange delivery of the product to GP clinics for administration. DUSC considered that this would be impractical and burdensome for pharmacies, and cannot be relied upon as the sole mechanism to manage the supply of the product. Additionally, the cost for pharmacies to provide this service was not accounted for by the sponsor. The ESC suggested that alternative models may include direct supply of the product to approved administration sites (i.e. GP clinics), or supply and administration by trained/accredited pharmacists, but noted that any supply model would have associated costs which have not been determined.

- 2.7 Under a Section 100 listing, the Commonwealth would fund the full cost of the medicine without fees, mark-ups or PBS patient co-payment. Dispensing sites could elect to charge private fees, although due to the reduced frequency of medication administration, these fees may be lower than those charged for existing listings. The ESC agreed that, assuming most patients transitioned to monthly dosing, there would likely be a reduction in private fees charged, and that this is a benefit for patients who currently choose not to be treated due to prohibitive private fees for existing treatments. However, the ESC noted that some patients are currently able to access a month's supply of sublingual buprenorphine/naloxone and therefore reduced frequency of attending a clinic or pharmacy may not be realised in these patients, although costs may still be lower.
- 2.8 Liaison with states and territories would be required to ascertain their willingness to offer this product through their existing OST programs as well as what individual assessment criteria for participation by prescribers and dosing sites might be needed. Time for liaison with states and territories would need to be factored into implementation of a positive recommendation for this product.

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

3 Background

Registration status

- 3.1 Prolonged release buprenorphine was submitted under the TGA/PBAC parallel process. At the time of PBAC consideration, the ratified resolution of the October 2018 Advisory Committee on Medicines (ACM) meeting were available. The ACM agreed with the proposed indication "...for the treatment of opioid dependence within a framework of medical, social and psychological treatment...for use in adults and adolescents aged 16 years and over."
- 3.2 The ACM agreed that patients should be stabilised on sublingual buprenorphine or buprenorphine/naloxone for at least 7 days before being transitioned to prolonged release buprenorphine, with no explicit requirement for patients to be on weekly injections prior to commencing once monthly treatment.

4 Population and disease

- 4.1 The target population in the submission is people with opioid dependence/opioid use disorder. Regular use of opioids can lead to opioid use disorder, which is a neurobehavioural chronic disorder with a natural history of relapse and remission, characterised by a problematic pattern of opioid use despite adverse social, psychological, and/or physical consequences. DUSC noted that the demographics of opioid misuse are changing, with increasing misuse of prescription opioids in place of illicit opioids.

- 4.2 Evidence-based interventions for opioid dependence include opioid withdrawal (detoxification), medication assisted treatment, psychosocial interventions and antagonist-assisted treatment either individually or in combination. Medication assisted treatment involves treatment of opioid dependence with a legally obtained, orally administered, long-lasting opioid which eliminates withdrawal symptoms and cravings or blocks the euphoric effect of opioid use.
- 4.3 Currently, three medications are PBS listed in Australia for long-term maintenance treatment for patients with opioid dependence (methadone, sublingual buprenorphine, and sublingual buprenorphine/naloxone). The submission claimed that prolonged release buprenorphine would provide an alternative treatment option for people with opioid dependence. The ESC agreed that there is a clinical place for prolonged release buprenorphine in certain patient populations with opioid use disorder, particularly as there are currently patients who choose not to be treated for opioid use disorder under the current pharmacy-based model due to perceived social unacceptability, and such patients may be more willing to seek treatment through a practice model delivered through general practice, if that was the model of care under which prolonged release buprenorphine was to be made available.

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

5 Comparator

- 5.1 The submission nominated sublingual buprenorphine/naloxone as the main comparator (therapy most likely to be replaced in practice). This was appropriate.
- 5.2 The submission also nominated RBP-6000, an alternative subcutaneous depot preparation of buprenorphine, as a near-market comparator (same drug with similar routes of administration). The sponsor stated that RBP-6000 has been submitted to the TGA for registration. This was appropriate.
- 5.3 Methadone may be considered an alternative comparator as a therapy that may be replaced by prolonged release buprenorphine, however was not nominated in the submission.
- 5.4 The ESC agreed sublingual buprenorphine/naloxone was a suitable main comparator, and that other opioid substitution therapies including methadone and buprenorphine could also be considered therapies likely to be replaced.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician at the hearing presented a brief overview the clinical data and discussed the importance of retention in

treatment for opiate dependence. The clinician further presented examples of an implementation model from a NSW Health perspective. The PBAC considered that the hearing was informative however it did not substantially address how prolonged release buprenorphine would be implemented under current arrangements.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from three organisations via the Consumer Comments facility on the PBS website. The comments described a range of anticipated social benefits of treatment with prolonged release buprenorphine including a reduction in dispensing fees and a lessening of the stigma and limitations that are associated with supervised dosing. The comments noted prolonged release buprenorphine would be another treatment option and not a replacement for all existing opiate dependence treatments.

Clinical trials

- 6.3 The submission was based on a series of comparisons between prolonged release buprenorphine and nominated comparators:
- One head-to-head comparison of the percent of urine samples negative for illicit opioids with prolonged release buprenorphine versus sublingual buprenorphine/naloxone in patients with moderate to severe opioid use disorder (HS-11-421) and an additional single arm open label safety study examining the long term effects of treatment with prolonged release buprenorphine in patients with opioid use disorder (HS-14-499).
 - One indirect comparison of the percent of urine samples negative for illicit opioids with prolonged release buprenorphine (HS-11-421) versus RBP-6000 (NCT02357901).
- 6.4 Details of the studies presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Prolonged release buprenorphine studies		
HS-11-421	A Phase III, Randomised, Double-Blind, Active-Controlled, Parallel Group, Multicenter Trial Assessing the Efficacy and Safety of a Once Weekly and Once Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder Lofwall MR, Walsh SL, Nunes EV et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of OUD: A Randomised Clinical Trial.	April 2018 <i>JAMA Intern Med</i> 2018; 178(6):764-773
HS-14-499	An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once Weekly and Once Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder.	June 2017
Subcutaneous buprenorphine depot (RBP-6000) studies		
RB-US-13-0001	Phase 3 randomised placebo-controlled trial designed to assess the efficacy, safety, and tolerability of RBP-6000 compared to placebo in treatment seeking adults with a diagnosis of opioid use disorder	Clinicaltrials.gov (NCT02357901)

Source: Table 23, p.32 of the submission; Appendix A of the submission

6.5 The key features of the included studies are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Prolonged release buprenorphine						
HS-11-421	428	R, DB, MC, AC 24 weeks	Low	Opioid use disorder	Percent urines negative for illicit opioids	Used to inform proportions of patients 'clean' versus 'using' in health states
HS-14-499	227	OL 48 weeks	High	Opioid use disorder	Quality of life (EQ-5D)	Used to derive health state utilities for sensitivity analysis
RBP-6000 (subcutaneous buprenorphine depot)						
NCT02357901	504	R, DB, MC, PC	Unclear	Opioid use disorder	Percent urines negative for illicit opioids	Not used

Source: Table 23, p.32; Table 24, p.37 of the submission; Table 3, p.8 Appendix A of the submission.

Abbreviations: R, randomised; DB, double blind; MC, multi-centre; AC, active controlled, OL, open label; PC, placebo controlled

Comparative effectiveness

6.6 The percentage of urine samples negative for illicit opioids, using primary imputation for missing urine test results (assuming missing values were positive) from trial HS-11-421 is summarised in the table below.

Table 4: Percentage urine samples negative for illicit opioids, without self-reported opioid use (ITT with imputed data; primary efficacy variable for the EU)

Prolonged release buprenorphine Mean (SE)	Sublingual buprenorphine/ naloxone Mean (SE)	LS mean difference (95% CI)	p-value (non-inferiority)
35.1 (2.47)	28.4 (2.50)	6.7 (-0.1, 13.6)	<0.001

Source: Table 39, p.79 of the submission; Table 13, p.79 HS-11-421 CSR.

Note: Standard errors were calculated during the evaluation.

6.7 Prolonged release buprenorphine demonstrated a numerically higher mean for the percentage of urine samples negative for illicit opioids compared with sublingual buprenorphine/naloxone. The lower bound of the 95% confidence interval was above the predefined non-inferiority margin of 11%. Based on this, prolonged release buprenorphine was determined to be non-inferior to sublingual buprenorphine/naloxone. The ESC recalled that mean percent urine samples negative for opiates was the outcome measure used in the November 2005 PBAC consideration of sublingual buprenorphine/naloxone.

6.8 The primary efficacy variable for the FDA was the responder rate. To be considered a responder for study Phase 1, the subject had to have no evidence of illicit opioids use at sample week 13 and no evidence of illicit opioids use for at least two out of the three sample weeks from week 10 to week 12. To be a responder for study Phase 2, the subject had to have no evidence of illicit opioids use at month 6 and no evidence of illicit opioids use in five out of the six illicit opioids use assessments in study Phase 2. To be a responder for the study, the subject must have been a responder for both study phases. For the FDA endpoint, evidence of illicit opioid use was defined as a positive urine toxicology result or a self-reported illicit opioid use.

6.9 Response rates for trial HS-11-421 are summarised in the table below.

Table 5: Responder rate, study Phase 1 and Phase 2 (ITT; primary efficacy endpoint for the FDA)

Prolonged release buprenorphine n/N (%)	Sublingual buprenorphine/ naloxone n/N (%)	Proportion difference (95% CI)	p-value (non-inferiority)
37/213 (17.4)	31/215 (14.4)	3.0 (-4.0, 9.9)	<0.001

Source: Table 37, p.78 of the submission; Table 11, p.77 HS-11-421 CSR.

6.10 The response rate for the study was 17.4% in the prolonged release buprenorphine treatment arm, and 14.4% in the sublingual buprenorphine/naloxone treatment arm. Given the lower limit of the 95% CI for response rate (-4.0%) was greater than the predefined non-inferiority margin of -10%, non-inferiority of prolonged release buprenorphine to sublingual buprenorphine/naloxone was met.

6.11 The cumulative distribution function is a continuous plot of the proportion of patients at each point along a continuum, who experience a percentage of negative urine samples at that point or lower. It allows the entire distribution of responses for the treatment and control group to be presented. Support for clinical efficacy is implied by greater separation of the cumulative distribution functions in the hypothesised direction. The null hypothesis of no difference in the cumulative distribution function of the percent of urine samples that were negative for illicit opioids from sample weeks 5-25 from trial HS-11-421 was tested at the 5% significance level using the Wilcoxon Rank-Sum test, summarised in the table below.

Table 6: Analysis results for cumulative distribution function of percentage of urine samples negative for illicit opioids (ITT population)

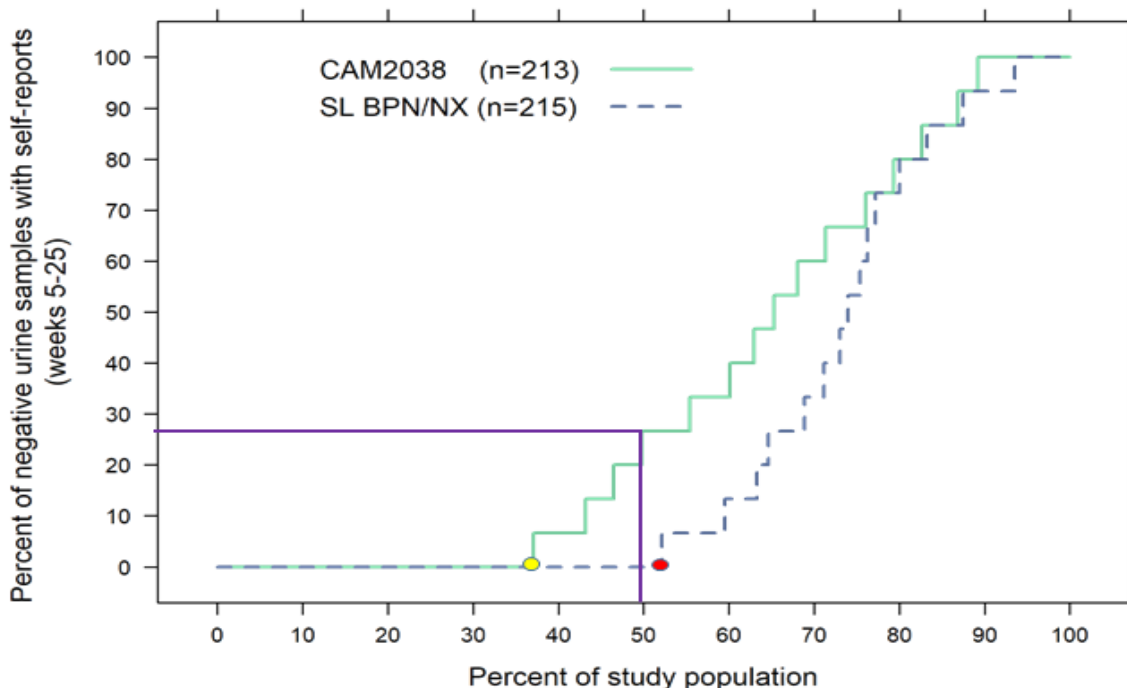
	Prolonged release buprenorphine	Sublingual buprenorphine/naloxone	Wilcoxon Rank-Sum test	
			Z-score	p-value
Including self-reported opioid use (FDA; weeks 5-25)				
Mean (SE)	35.1 (2.55)	26.7 (2.53)	-	-
Median [range]	26.7 [0-100]	0 [0-100]	2.86	0.004
Not including self-reported opioid use (EU; weeks 5-25)				
Mean (SE)	35.8 (2.56)	27.7 (2.55)	-	-
Median [range]	26.7 [0-100]	6.7 [0-100]	2.66	0.008

Source: Table 41, p.83 of the submission; Table 15, p.84 HS-11-421 CSR

Note: Standard errors calculated during the evaluation

6.12 The cumulative distribution function of percent urine samples negative for illicit opioids over weeks 5-25 (incorporating self-reported opioid use) from trial HS-11-421 is presented in the figure below (FDA analysis).

Figure 1: Cumulative distribution function of percent of urine samples negative for illicit opioids supported by self-report opioid use weeks 5 to 25 (ITT population, includes subjects' self-reported opioid use [FDA])

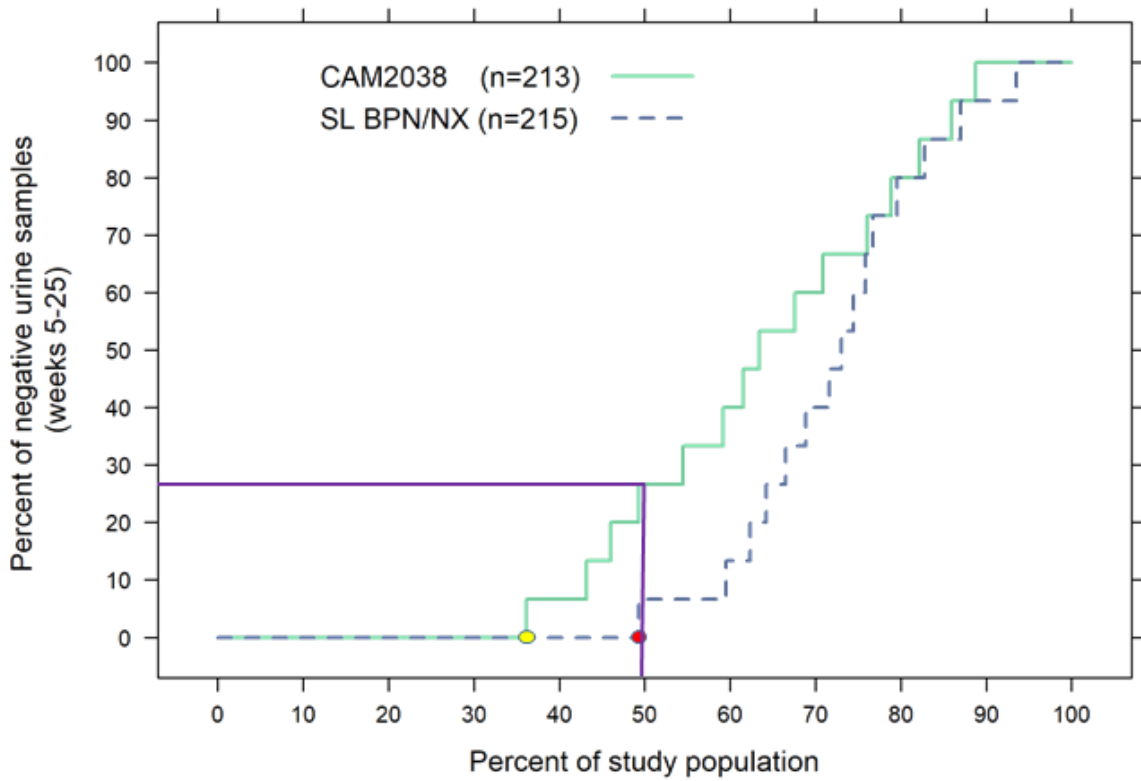


Source: Figure 12, p.80 of the submission

Notes: CAM2038= prolonged release buprenorphine; SL BPN/NX= sublingual buprenorphine/naloxone

6.13 The cumulative distribution function of percent urine samples negative for illicit opioids over sample Weeks 5-25 from trial HS-11-421 is presented in the figure below (EU analysis). This analysis did not incorporate self-report of illicit opioid use.

Figure 2: Cumulative distribution function of urine samples negative for illicit opioids sample weeks 5-25 (ITT population, without subjects' self-reported opioid use [EU])



Source: Figure 13, p.82 of the submission

Notes: CAM2038= prolonged release buprenorphine; SL BPN/NX= sublingual buprenorphine/naloxone

- 6.14 In both the analyses with and without self-reported opioid use, prolonged release buprenorphine was found to be statistically significantly superior to sublingual buprenorphine/naloxone on the cumulative distribution function of the proportion of opioid negative urine samples.
- 6.15 The ESC considered that the cumulative distribution function as an outcome measure was difficult to interpret and the clinical significance of this outcome was uncertain.
- 6.16 Sustained abstinence of opioid use was defined as no opioid use from randomisation through the rest of treatment period for at least two months. Results for the analysis of time to sustained abstinence of opioid use are summarised in the table below.

Table 7: Patients with sustained abstinence of opioid use

	Prolonged release buprenorphine n/N (%)	Sublingual buprenorphine/naloxone n/N (%)	p-value (log rank test)
Subjects with sustained abstinence of opioid use	39/213 (18.31)	30/215 (13.95)	0.221

Source: Table 42, p.86 of the submission; Table 17, p.86 HS-11-421 CSR

6.17 Although the number and proportion of patients with sustained abstinence was numerically higher in the prolonged release buprenorphine treatment group compared with the sublingual buprenorphine/naloxone treatment group, this difference was not statistically significant. Because this endpoint did not meet the predefined hypothesis for superiority of prolonged release buprenorphine, ordered hypothesis testing was stopped after this endpoint was tested (EMA). Outcomes assessed beyond this were considered exploratory only.

6.18 Results for the analysis of percentage of patients remaining in the study (retention rate) from trial HS-11-421 are summarised in the table below.

Table 8: Percentage of patients remaining in the study (retention rate; ITT)

	Prolonged release buprenorphine n/N (%)	Sublingual buprenorphine/naloxone n/N (%)	Proportion difference (95% CI)	p-value (non-inferiority)
Subjects remaining in study	121/213 (56.8)	126/215 (58.6)	-1.8 (-11.2, 7.6)	0.006

Source: Table 43, p.87 of the submission; Table 18, p.86 HS-11-421 CSR

6.19 In both treatment groups, just over half of all subjects remained in the study, with retention rates of 56.8% for the prolonged release buprenorphine treatment group and 58.6% for the sublingual buprenorphine/naloxone treatment group. The difference between treatment groups was -1.8% (95% CI: -11.2%, 7.6%), and the prolonged release buprenorphine group was nominally non-inferior to the sublingual buprenorphine/naloxone group (non-inferiority margin of 15% for the EMA analysis).

6.20 In study HS-14-499, administration of the EQ-5D-5L health questionnaire was introduced by a protocol amendment and baseline values are not available; the earliest time point available was Day 113 (approximately Week 16). The number of subjects with EQ-5D-5L scores varied widely by time point (ranging from 1-167 completions at each time point).

6.21 Utility weights used in a sensitivity analysis in the economic model were derived from all responses to the EQ-5D in study HS-14-499, by whether the patient had a urine sample positive for illicit opioids at that time or not. Utility weights were derived using the English EQ-5D-5L value set (Devlin et al., 2018). The mean weights were 0.92 and 0.87, for people with negative and positive urine samples respectively.

6.22 The submission presented a naïve indirect comparison between prolonged release buprenorphine and near market comparator RBP-6000. Due to differences in trial

design, including lack of a common reference arm, the submission suggested that studies HS-11-421 and RB-US-13-0001 were not comparable, and a formal indirect comparison was not appropriate. This was reasonable.

- 6.23 A comparison of the proportions and cumulative distribution function of the proportions of urine samples negative for illicit opioid use with self-reports for studies HS-11-421 and RB-US-13-0001 are summarised in the table below.

Table 9: Proportions of urine samples negative for illicit opioid use with self-reports

Trial ID Treatment	HS-11-421		RB-US-13-0001		
	Prolonged release buprenorphine	Sublingual buprenorphine / naloxone	RBP-6000 300/100	RBP-6000 300/300	Placebo
N	213	215	196	194	99
Percentage of urine samples negative for opioids with self-reports					
Percentage mean (SD)	35.1% (37.2)	26.7% (37.2)	43% (38)	41% (40)	5% (17)
Median	26.7%	0%	33%	30%	0

Source: Table 8, p.20, Appendix A - Comparison of CAM2038 vs RBP-6000 FINAL; Table 15 of HS-11-421 CSR; RB-US-13-0001: Data extracted from Braeburn FDA Briefing Document: Figure 16, pg 71 and Table 12, pg 72

Abbreviations: BMI, body mass index; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone

- 6.24 The cumulative distribution function of the proportions of urine samples negative for illicit opioid use with self-reports and the overall proportions of urine samples negative for illicit opioid use favoured RBP-6000 compared to prolonged release buprenorphine. However, the differences were small and both distributions followed similar trajectories over 24 weeks of treatment.
- 6.25 Overall, the efficacy of prolonged release buprenorphine and RBP-6000 appeared similar. However, given the differences in study design comparisons of efficacy between studies HS-11-421 and RB-US-13-0001 should be interpreted with caution. The ESC did not consider that this comparison was informative.

Comparative harms

- 6.26 Overall, the most common drug-related adverse events in trial HS-11-421 were injection site pain (8.2%), constipation (5.8%), injection site pruritus (5.8%), injection site erythema (5.1%), injection site swelling (3.5%), headache (3.0%), injection site reaction (2.8%), and nausea (2.8%). Incidences of individual adverse events related to study drug were generally comparable between prolonged release buprenorphine and sublingual buprenorphine/naloxone. Apart from injection site reactions, the adverse events were consistent with the known safety profile of buprenorphine.
- 6.27 A total of 88 (20.6%) subjects had at least 1 injection site treatment-emergent adverse event during the study, with 48 (22.3%) in the sublingual buprenorphine/naloxone group and 40 (18.8%) in the prolonged release buprenorphine group. The most common injection site adverse events were injection site pain (8.4%), injection site pruritus (6.1%), and injection site erythema (5.6%). Five subjects (3, sublingual buprenorphine/naloxone; 2, prolonged release buprenorphine) had an injection site ulcer (3, mild; 2, moderate).

- 6.28 In regards to adverse events of special interest, there were 5 cases of overdose in trial HS-11-421 (4, accidental; 1, intentional), all of which were in the sublingual buprenorphine/naloxone group. The 4 cases of accidental overdose involved heroin (3 subjects) or clonazepam (1 subject). The intentional overdose involved doxepin, prazosin, and venlafaxine. Four of the cases of overdose (3 accidental; 1 intentional) were considered serious adverse events because they were life-threatening.
- 6.29 In study HS-14-499, 60 (26.4%) subjects had at least 1 study drug-related adverse event. The most common drug-related adverse events were injection site pain (15.4%), injection site swelling (11.5%), and injection site erythema (9.3%). All of the drug-related adverse events, except for one event of injection site pain, were mild or moderate in intensity.
- 6.30 In study RB-US-13-0001, the most frequently reported adverse events ($\geq 5\%$ of patients) associated with subcutaneous depot buprenorphine were severe headache (8.9%), constipation (8.7%), nausea (8.4%), injections site pruritus (7.9%), vomiting (7.4%), insomnia (7.4%), upper respiratory tract infection (6.7%), nasopharyngitis (5.2%), fatigue (5.0%) and injection site pain (5.4%). This was similar to the most frequently reported adverse events reported in study HS-11-421. However, larger proportions of patients treated with prolonged release buprenorphine in study HS-11-421 reported injection site erythema and injection site pain compared to those treated with RBP-6000 in study RB-US-13-0001.
- 6.31 The ESC considered the comparative harms were acceptable and supported the claim of non-inferior safety.

Benefits/harms

- 6.32 A summary of the comparative benefits and harms for prolonged release buprenorphine versus sublingual buprenorphine/naloxone is presented in the table below.

Table 10: Summary of comparative benefits and harms for prolonged release buprenorphine and sublingual buprenorphine/naloxone in trial HS-11-421

	Prolonged release buprenorphine	SL buprenorphine/naloxone	Difference (95% CI)	z-score (p-value)
Benefits				
Percentage urine samples negative for illicit opioids (excluding self-reports)	35.1%	28.4%	6.7% (-0.1, 13.6)	(<0.001) (non-inferiority)
Responder rate (including self-reports)	17.4%	14.4%	3.0% (-4.0, 9.9)	(<0.001) (non-inferiority)
Percentage of urine samples negative for illicit opioids for half of all patients treated (CDF)	26.7%	6.7%	20%	2.66 (0.008)
Patients with sustained abstinence of opioid use	18.31%	13.95%	4.36%	(0.221)
Patients remaining on treatment	56.8%	58.6%	-1.8% (-11.2, 7.6)	(0.006)
Harms	Prolonged release buprenorphine, n/N	SL buprenorphine/naloxone, n/N	Event rate/100 patients	
			Prolonged release buprenorphine	SL buprenorphine/naloxone
Treatment related injection-site adverse event	36/213	Not relevant	17	Not relevant
Nausea	9/213	3/215	4	1
Headache	8/213	5/215	4	2

Source: Table 37, p.78; Table 39, p.79; Table 42, p.86; Table 44, p.89 of the submission; Table 11, p.77 Table 24, p.107 HS-11-421 CSR
Abbreviations: CDF, cumulative distribution function; SL, sublingual; NS, no statistically significant difference.

6.33 On the basis of the direct evidence presented in the submission, over a period of 24 weeks:

- There was no difference between treatments in the proportion of patients with urine samples negative for illicit opioids;
- There was no difference between treatments in proportion of patients achieving a response (including self-reported opioid use);
- Half of all patients treated with prolonged release buprenorphine would have at least 1 out of every 4 (26.7%) urine samples negative for illicit opioids, whereas half of all patients treated with sublingual buprenorphine/naloxone would have around 1 out of every 15 (6.7%) urine samples negative for illicit opioids;
- There was no difference between treatments in the proportion of patients abstaining from opioid use;
- There was no difference between treatments in the percentage of patients remaining on treatment.

6.34 For every 100 patients treated with prolonged release buprenorphine:

- 17 patients would experience injection-site adverse events. Patients receiving sublingual buprenorphine/ naloxone in the trial received placebo injections, therefore injection-site adverse events experienced by these patients during the trial would not be realised in practice;
- An additional 3 patients would experience nausea compared with sublingual buprenorphine/naloxone; and
- An additional 2 patients would experience headache compared with sublingual buprenorphine/naloxone.

Clinical claim

6.35 The submission described prolonged release buprenorphine as superior in terms of effectiveness compared with sublingual buprenorphine/naloxone, with a comparable safety profile. The ESC considered the claim of superior effectiveness was not well supported as non-inferiority was demonstrated for the clinical outcomes of proportion of patients with urine samples negative for illicit opioids, response rate, abstinence rate, and retention to treatment. Superiority was only demonstrated based on cumulative distribution function (CDF), however ESC consider this was difficult to interpret and of uncertain clinical importance.

6.36 The ESC instead accepted that prolonged release buprenorphine is non-inferior to sublingual buprenorphine/naloxone in terms of both efficacy and safety.

6.37 The submission did not make a therapeutic conclusion regarding the comparative efficacy of prolonged release buprenorphine and near market comparator RBP-6000 (a depot formulation of buprenorphine), due to poor exchangeability of the trials. The ESC agreed that it was reasonable that no clinical claim was made against RBP-6000.

6.38 The submission also claimed that prolonged release buprenorphine would improve treatment retention, negate diversion, and increase system capacity for treatment, outcomes which were not able to be measured in the clinical studies. These additional benefits are difficult to quantify and the submission provided no evidence to support these claims. Whilst it is conceivable that these benefits may be somewhat realised in clinical practice, the size of these benefits is unknown, and thus some more exploration around this is required before a benefit is ascribed to prolonged release buprenorphine. Access to prolonged release buprenorphine is unlikely to increase system capacity for treatment as restrictions on prescriber and dosing site numbers will still apply.

6.39 The PSCR acknowledged that benefits not captured in the trial (improved retention in treatment, reduced risk of diversion, increased system capacity to benefit) were difficult to quantify, but maintained that they would apply in clinical practice. The ESC did not accept the claim of superiority based on these additional benefits.

6.40 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data presented.

6.41 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.42 The submission presented a stepped economic evaluation of prolonged release buprenorphine compared with sublingual buprenorphine/naloxone for the treatment of opioid use disorder. The economic evaluation was based on the mean percentage of urine samples negative for illicit opioids (EU primary noninferiority outcome, excluding self-report of illicit opioid use) measured in the direct randomised trial (HS-11-421) and other modelled variables. The type of economic evaluation presented was a cost-utility analysis.

Table 11: Summary of model structure and rationale

Component	Summary
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Cost per additional time not using ('clean'); quality-adjusted life years
Time horizon	5 years
Methods used to generate results	Markov cohort expected value analysis (with half cycle correction)
Treatments	Prolonged release buprenorphine, sublingual buprenorphine/naloxone
Health states	Four health states: initial treatment episode, subsequent treatment episode, non-adherent, death
Cycle length	28 days
Transition probabilities	Probability patients are 'clean' or 'using' whilst persistent to medication-assisted treatment - Treatment dependent based on HS-11-421 data Probability of remaining persistent to treatment - Comparison of prolonged release buprenorphine data (clinical trial and observational) with rates of persistence to MAT in Australian clinical practice (Burns 2014) Probability of returning to MAT after a period of discontinuation - Same for both treatment groups based on data observed for 262 Australian MAT patients over a 5 year follow-up period (Bell 2006) Probability of death - Same for both treatment groups but lower for patients persistent to MAT. Based on Australian data for 3349 patients in and out of MAT (Bell 2009)
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro

Source: Table 62, p.144 of the submission.

Abbreviations: MAT, medication assisted treatment

6.43 All patients start the model in the adherent to treatment health state – with a proportion of patients continuing to use illicit opioids. During each four-week cycle, patients may remain adherent to treatment, become non-adherent to treatment or die. The probability of death is based on mortality rates in a cohort of patients receiving buprenorphine treatment between June 2002 and June 2006 in NSW, Australia.

6.44 The non-adherent state is a tunnel health state to allow probabilities of treatment re-entry at exactly one, two, three and five years post-treatment cessation to be applied. Patients in the non-adherent state have a higher risk of death. Patients in the subsequent treatment episode state have the same probabilities of becoming non-adherent and dying as patients in the initial treatment episode state. Patients cycle through these health states in 28-day cycles for five years.

6.45 Key drivers of the economic model are summarised in the table below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Retention benefit associated with prolonged release buprenorphine	The probability of remaining on treatment over time for sublingual buprenorphine/naloxone and prolonged release buprenorphine was derived using the retention curve from Burns et al. (2014) compared with the retention curve from the HS-14-499 open-label study to calculate a hazard ratio for retention with prolonged release buprenorphine compared to sublingual buprenorphine/naloxone. Burns et al. (2014) was a descriptive study, which did not take into account buprenorphine dose, a critical factor that affects treatment retention. The resulting hazard ratio (3.85) was applied over the first 36 weeks of treatment, after which the hazard ratio reverts to 1. No justification was provided for the application of improved retention over 36 weeks. The persistence curves for the remaining time on treatment are assumed to be the same as per Burns et al. (2015). Whilst some retention benefit associated with prolonged release buprenorphine may be achieved in practice, it is unlikely to be as significant as that applied in the model. The method used to derive the hazard ratio is associated with uncertainty; the treatment effects are drawn from very different data sources (one open label clinical study and one observational study) which may not be comparable and assumptions of the Cox proportional hazards model were not assessed. Given the differences in studies, particularly that one was a real-world observational study, the assumption of non-informative censoring is likely to be violated. This manufactured hazard ratio is unlikely to be representative of the true difference in treatment retention between sublingual buprenorphine/naloxone and prolonged release buprenorphine.	High; favours prolonged release buprenorphine
Inclusion of supervision costs of sublingual buprenorphine/naloxone	The model included private costs to patients for supervision of sublingual buprenorphine/naloxone, charged in community pharmacies and some public clinics. Whilst these costs are considered an important barrier to medication assisted treatment, their inclusion in the economic model may not be appropriate. Private costs to patients were not considered in the prolonged release buprenorphine treatment arm, despite dispensing sites still being able to charge private fees to patients being treated with prolonged release buprenorphine.	High; favours prolonged release buprenorphine
Health state costs	Health state costs used in the economic model were derived from a retrospective analysis of US health claims data which analysed healthcare resource utilisation according to adherence to medication assisted treatment (Tkacz et al., 2014). This is unlikely to be representative of health service use in Australia.	High; favours prolonged release buprenorphine
Costs of illicit opioid use	As a sensitivity analysis incorporating the broader societal costs of opioid use disorder, the model included the average cost of heroin use at \$186.40 per day for 25.2 days of a 28-day cycle (\$4697.28 per cycle) applied to the proportion of patients 'using' in each health state. It is unclear whether using the cost of heroin as a proxy for costs of all illicit opioid use was reasonable, particularly given the changing demographics of opioid use in recent years (increasing illicit use of prescription opioids).	High; favours prolonged release buprenorphine
Utilities	The model was moderately sensitive to the utility values used in the model (published utilities versus trial-based derived from study HS-14-499), and the	Moderate

Description	Method/Value	Impact
	proportion of utilities assigned to injecting versus non-injecting drug users. Given the higher proportion of injecting drug users in the Australian population, this could have been used to derive utilities, rather than an average (base case).	
Proportion of patients stabilized on the monthly formulation of prolonged release buprenorphine	The model assumed that after the initial treatment cycle where all patients in the prolonged release buprenorphine treatment arm were treated with the weekly formulation (4 weeks), 74.7% of patients would be stabilized on the monthly formulation. This reduced costs of administration of prolonged release buprenorphine.	Moderate; favours prolonged release buprenorphine

Source: Compiled during the evaluation

6.46 The results of the modelled economic evaluation are summarised in the table below.

Table 13: Results of the stepped economic analysis

Resource item	Prolonged release buprenorphine	Sublingual buprenorphine/naloxone	Increment	Incremental cost-effectiveness ratio
Step 1: Trial based evaluation including drug costs and supervision/administration costs. All patients compliant and adherent to treatment. Six month duration.				
Costs	\$ [redacted]	\$2,567	\$ [redacted]	\$ [redacted]
Time spent 'clean'	0.1600	0.1295	0.0305	
Step 2: Trial based evaluation with time spent clean transformed to quality adjusted life years and health state costs included^a				
Costs	\$ [redacted]	\$4,822	\$ [redacted]	\$ [redacted]
QALYs	0.3335	0.3271	0.0064	
Step 3: Modelled time horizon extrapolated to 1 year				
Costs	\$ [redacted]	\$10,298	\$ [redacted]	\$ [redacted]
QALYs	0.7123	0.6986	0.0136	
Step 4: Modelled time horizon extrapolated to 3 years				
Costs	\$ [redacted]	\$29,298	\$ [redacted]	\$ [redacted]
QALYs	2.0264	1.9876	0.0388	
Step 5: Modelled time horizon extrapolated to 5 years				
Costs	\$ [redacted]	\$46,353	\$ [redacted]	\$ [redacted]
QALYs	3.2061	3.1447	0.0614	
Step 6: Model treatment discontinuation from medication-assisted treatment (using retention curve from Burns et al., 2014)				
Costs	\$ [redacted]	\$48,432	\$ [redacted]	\$ [redacted]
QALYs	2.8900	2.8696	0.0203	
Step 7: Model retention benefit associated with prolonged release buprenorphine (apply hazard ratio of 3.85 to retention curve from Burns et al. (2014) for 9 cycles)				
Costs	\$ [redacted]	\$48,432	\$ [redacted]	\$ [redacted]
QALYs	3.0001	2.8696	0.1305	

Source: Table 80, p.175 of the submission; CAM2038 Section 3 TreeAge model.trex

^a Inclusion of health state costs in this step had no impact on the incremental cost of prolonged release buprenorphine because health state cost offsets are only realised in the model structure with retention benefits (Step 7)

The redacted table shows ICERs in the range of less than \$15,000/QALY to \$75,000/QALY - \$105,000/QALY.

6.47 Based on the economic model presented in the submission, treatment with prolonged release buprenorphine was associated with a cost per QALY of less than \$15,000 compared with sublingual buprenorphine/naloxone.

- 6.48 The steps incorporating the transformation to quality adjusted life years, the inclusion of health state costs, and the inclusion of the retention benefit had the largest impact on the stepped economic evaluation. The ESC considered that whilst a retention improvement was possible with prolonged release buprenorphine due to the nature of the formulation, this was not supported by the clinical trial evidence provided as this outcome measure demonstrated non-inferiority. As such, ESC considered that applying a hazard ratio of 3.85 for improved retention was unreasonable. The ESC further noted that for some patients, regular contact with a healthcare provider through receiving OST could improve retention, and therefore considered that the lack of regular contact with service providers resulting from the monthly administration of prolonged release buprenorphine may decrease long term retention.
- 6.49 Economic evaluations of treatments for substance use disorders frequently include a consideration of the broader societal impact of treating these disorders. This broader impact generally includes factors such as reduced crime, legal system costs, costs of incarceration and other unproductive distortions in the economy. In a sensitivity analysis, the economic model included the acquisition cost of heroin as a proxy measure of this broader societal impact. When these costs (\$186.40 per day applied the proportion “using”) were included in the economic evaluation, prolonged release buprenorphine became dominant (lower costs and higher benefits) compared with sublingual buprenorphine/naloxone. This analysis is dependent upon the assumption that the cost of heroin is a relevant proxy for the societal costs of illicit opioid use. The ESC considered that these costs were not reasonable particularly as the demographics of opioid misuse are changing, with increasing misuse of prescription opioids in place of illicit opioids.
- 6.50 The results of univariate and multivariate sensitivity analyses presented in the submission and conducted throughout the evaluation indicated that the model was most sensitive to the application of the retention benefit (both size of benefit and duration of application), utility values, the inclusion of the sublingual buprenorphine/naloxone supervision costs, and the healthcare resource use costs in the adherent and non-adherent health states. The PSCR stated that applying private costs in one arm of the model but not in the other arm of the model is a consequence of the bias which exists in clinical practice and not a bias of the economic model. The ESC advised that regardless of the practice model adopted, there will be private costs associated with accessing prolonged release buprenorphine. The magnitude of these costs will vary depending on the model of care, and as such cannot be quantified. Thus the ESC considered that differentially applying supervision costs was inappropriate and considered it more appropriate to remove supervision costs from both arms of the model.
- 6.51 The absence of retention benefits (HR=1) and removing the cost for supervision of sublingual buprenorphine/naloxone (as a private cost to patients) increased the ICER to \$105,000/QALY - \$200,000/QALY. When the retention benefit was included, health state resource use costs also had a large impact on the ICER.

- 6.52 The PSCR agreed the retention benefit has a high impact on the results of the model however, maintained that the application of persistence benefits in the model are appropriate given the available data analysis of Australian patients using sublingual buprenorphine reported in Burns et al., 2014 and prolonged release buprenorphine from the HS-14-499 open label trial. The ESC considered the use of these disparate data sources maximised any possible difference in retention between treatment types, one being a real world observational study over a ten-year period and the other a shorter duration open label clinical study which did not reflect the likely treatment model in the Australian setting (particularly noting that patients were unsupervised between doses, and that patients were compensated for time and expenses). Although an improved retention rate in treatment may occur in clinical practice, it was most likely overestimated in the economic model.
- 6.53 As the ESC was not satisfied that the clinical claim of superiority of prolonged release buprenorphine over sublingual buprenorphine/naloxone was supported, ESC instead considered that a cost-minimisation analysis would be more appropriate. As prolonged release buprenorphine dose regimens are not fully interchangeable with sublingual dose forms, and because the dosing of both products is individualised to each patient’s needs, the calculation of equi-effective doses between the formulations is challenging. The most practical method for a cost-minimisation analysis would be using annual drug costs on a cost per day basis.
- 6.54 Alternatively, if a claim of superior efficacy compared to sublingual buprenorphine/naloxone was accepted, the ESC considered that a more realistic base case would be to reduce the retention benefit hazard ratio (from 3.85 to 1.25), reduce the duration of the retention benefit (from 9 cycles to 3-6 cycles), decrease health state costs by 50%, and remove supervision costs. The results of the ESC revised base case are presented in the table below. The pre-PBAC response maintained that supervision costs should be included.

Table 16: ESC respecified base case

Retention benefit	Duration of retention benefit	Health state costs	Sublingual BPN/NX supervision cost	Incremental costs	Incremental QALYs	ICER
Hazard ratio 1.25	3 cycles (12 weeks)	Decreased 50%	Removed	\$ [REDACTED]	0.0339	\$ [REDACTED]
	6 cycles (24 weeks)	Decreased 50%	Removed	\$ [REDACTED]	0.0399	\$ [REDACTED]

Source: Calculated during the evaluation using 'CAM2038 Section 3 TreeAge model.trex'

Abbreviations: BPN, buprenorphine; HR, hazard ratio; ICER, incremental cost effectiveness ratio; NX, naloxone; QALYs, quality adjusted life years;

The redacted table shows ICERs in the range of \$105,000/QALY - \$200,000/QALY.

Drug cost/patient/year

- 6.55 The estimated drug cost for prolonged release buprenorphine per patient per year was \$ [REDACTED] (based on 365 days of use at a daily cost of \$ [REDACTED]). The drug cost was not impacted by the proportion of patients treated weekly compared to monthly doses.
- 6.56 The estimated drug cost for sublingual buprenorphine/naloxone per patient per year was \$3,956.6 (based on 365 days of use at a daily cost derived from the current ex-manufacturer price of \$10.84).
- 6.57 The proposed price per day for prolonged release buprenorphine represents a premium of [REDACTED]% over the current daily price of sublingual buprenorphine/naloxone. The ESC considered that a price premium of this magnitude over sublingual buprenorphine/naloxone was not justified.
- 6.58 The PBAC noted in its pre-PBAC response the sponsor proposed a price reduction from \$ [REDACTED] per day to \$ [REDACTED] per day, representing a lower premium over sublingual buprenorphine/naloxone of [REDACTED]%. The PBAC considered that the incremental benefits of prolonged release buprenorphine were not quantified in the submission and therefore the revised price premium of [REDACTED]% over sublingual buprenorphine/naloxone was not justified.

Estimated PBS usage & financial implications

- 6.59 This submission was considered by DUSC.
- 6.60 The submission used a market share approach to estimate the use and financial implications of listing prolonged release buprenorphine on the PBS for the treatment of opioid use disorder, as summarised in the table below.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of prolonged release buprenorphine						
Cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Co-payments	N/A	N/A	N/A	N/A	N/A	N/A
Cost offsets for substituted therapies	-\$976,282	-\$4,937,146	-\$8,810,946	-\$11,879,018	-\$12,010,082	-\$12,141,123
Net financial implications						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 96, p192, and Table 98, p194-5 of the submission

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year, and the net cost to the PBS/RPBS was \$20 - \$30 million per year.

- 6.61 PBS utilisation data are not available for the individual medication assisted therapies. The data used to inform the market share approach were drawn from the National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) snapshot day 2017 (to estimate patient numbers) which were compared with actual PBS expenditure (Medicare Australia). The estimates of utilisation and financial implications associated with listing prolonged release buprenorphine on the PBS were highly uncertain. DUSC highlighted the implicit assumptions of NOPSAD, including that the snapshot day is reflective of all days of the year, that differences between NOPSAD and PBS data are equally distributed between all therapies, and that there is no wastage. Despite these limitations, DUSC agreed with the evaluation that NOPSAD data is generally considered to be the best national estimate of the number of patients in treatment on an average day; and was not aware of a more reliable data source that could be used as a basis for estimating use.
- 6.62 The overall market for medication assisted treatment for opioid use disorder for the first six years of listing was estimated by linear extrapolation of the NOPSAD data (2012-2017), assuming no additional increase in market size due to the listing of prolonged release buprenorphine. Based on the trend, DUSC considered a linear extrapolation might not have been the most appropriate projection. DUSC also considered that additional market growth beyond the projections would be possible as a result of listing prolonged release buprenorphine; as a significant proportion of patients with opioid use disorder are currently untreated. Some of these patients may be unwilling to seek treatment due to social stigma associated with the current pharmacy-based model, particularly as the demographics of opioid misuse are changing, with increasing misuse of prescription opioids in place of illicit opioids. DUSC was of the view that if a practice model were adopted that was primarily GP based, there may be patients with untreated opioid use disorder who may seek treatment due to increased acceptability of the practice model and convenience of monthly dosing.
- 6.63 The actual PBS expenditure was found to be significantly lower than the predicted expenditure based on the patient numbers in the NOPSAD data (by a factor of 0.64). It was unclear why the PBS expenditure was lower than the predicted expenditure based on patient numbers. The financial estimates rely heavily on the relationship between these two data sources, with the lower expenditure entirely attributed to reduced compliance.
- 6.64 The PSCR justified the application of this compliance factor as an adjustment for the discrepancy in actual PBS expenditure versus expenditure derived from the number of patients per NOPSAD data. While the factor was labelled “compliance”, the sponsor acknowledged that this discrepancy could be due to compliance, dose or other factors. DUSC considered that the compliance factor of 0.64 was unreliable, given the differences in mode of action and route of administration between treatments.

- 6.65 The submission further adjusted the estimated cost of prolonged release buprenorphine for a claimed improvement in treatment retention modelled in the cost effectiveness analysis. Based on the ratio of time spent in adherent health states between prolonged release buprenorphine and sublingual buprenorphine/naloxone treatment regimens in the economic model, an additional factor of 1.7 was applied to the cost per patient per year ($0.64 \times 1.7 = 1.088$); i.e. 1.7 weeks of prolonged release buprenorphine treatment for every week of sublingual buprenorphine, sublingual buprenorphine/naloxone or methadone treatment. The derivation and application of the retention benefit in the economic model was associated with significant uncertainty, and likely overestimated any retention benefit associated with prolonged release buprenorphine. As a result, this is likely to have substantially overestimated the cost of listing prolonged release buprenorphine on the PBS. DUSC further noted that the population in the key clinical trials differed from Australian practice, including that patients were unsupervised between doses, and that patients were compensated for time and expenses. These factors made the retention benefit unreliable.
- 6.66 The estimated financial implications of listing prolonged release buprenorphine on the PBS were most sensitive to the assumed uptake rate. The PSCR commented that modest uptake of 10% was applied given the potential challenges with infrastructure, distribution, limited switching from methadone and treatment adoption. DUSC considered there was no justification for why the uptake would cease to increase after Year 3. In the context of a product claiming superior effectiveness, it is unusual that the estimated uptake would be as low as 0.85% to 10% per annum.
- 6.67 The submission assumed that costs associated with administration and management of opioid use disorder would be similar between treatments and assumed negligible changes to the MBS. Given the requirement for prolonged release buprenorphine to be administered by a health professional at least monthly (and weekly in some patients), there is likely to be an MBS cost associated. DUSC considered that this would particularly be evident in the stabilisation phase, where patients would have more regular GP consultations.
- 6.68 The rates of substitution from other MAT to prolonged released buprenorphine are likely to be impacted significantly by the practice model adopted for this product, such as whether the product can be supplied through a patient's usual dispensing site or whether access will be limited to use in alcohol and drug treatment clinics or other public or private health clinics. As the submission did not propose a mechanism by which this listing could be implemented within existing frameworks, the impact of the implementation approach is not able to be determined in the context of utilisation and financial implications. DUSC considered that displacement of existing medication assisted treatments for opioid use disorder is uncertain and is likely to depend upon the adequate resolution of the quality use of medicines issues outlined below, the TGA's advice on how to initiate treatment, and the private fees charged to patients for accessing prolonged release buprenorphine.

- 6.69 Overall, the estimated cost of listing prolonged release buprenorphine on the PBS was uncertain and most likely underestimated, and the costs of listing may be higher than estimated in the submission if uptake of prolonged release buprenorphine is higher than assumed.

Quality Use of Medicines

- 6.70 No quality use of medicines issues were identified in the submission. A range of QUM issues were identified through the evaluation and by DUSC, with no accompanying QUM plan provided by the sponsor. The resolution of these QUM issues is critical for estimating utilisation of prolonged release buprenorphine in practice and is likely to influence whether this product would be prescribed in place of currently available opioid substitution therapies.
- 6.71 Given the long acting formulation of prolonged release buprenorphine, it may be difficult to reverse the opioid effects in emergency situations, including accidental overdose. DUSC also highlighted that under the current opioid substitution model, if a patient presents at a dispensing site for a daily dose whilst intoxicated with alcohol or other drugs, the daily dose of methadone/buprenorphine is withheld. However, due to the long acting formulation of prolonged release buprenorphine, there is a decreased ability for health practitioners to manage the risk of CNS depression in patients engaging in polydrug use.
- 6.72 Evidence was provided suggesting that unsupervised dosing was as effective as supervised dosing. However, the Australian study in question excluded patients with more complex care needs. Hence, while the submission suggested that eliminating the requirement for daily dosing is a potential benefit of treatment with prolonged release buprenorphine, DUSC considered that there are some patients who may have an improved therapeutic response to opioid substitution therapies as a result of regular interaction with a healthcare provider.
- 6.73 Patients on buprenorphine who require pain management may have specific requirements and it is unclear how this will be managed in the context of prolonged release buprenorphine. Pain management should be carefully monitored, since patients with opioid use disorder often have decreased pain tolerance and cross-tolerance to opioid analgesics, resulting in a need for higher opioid doses and shorter dosing intervals. DUSC considered that this issue should be addressed by the sponsor in a QUM plan.
- 6.74 DUSC further considered that the safety of stopping treatment with, or weaning from, prolonged release buprenorphine was unclear and should be addressed.
- 6.75 Five clinical trial patients reported an injection site ulcer. These patients were enrolled at the same site; the ulcerative injection site reactions were all attributed to inappropriate injection technique by the same individual. The nature of this risk and the relevance for clinical practice is unclear. Further, the submission does not detail

any physician education programs regarding the correct injection technique required for safe administration of prolonged release buprenorphine.

- 6.76 It is unclear what risk would be posed to patients by intravascular injection. No human studies of the risks and effects of intravascular injection of prolonged release buprenorphine were available, however the ACM agreed that a boxed warning regarding venous occlusion on intravenous administration was appropriate.
- 6.77 DUSC considered that the most practical model of implementation for prolonged release buprenorphine is for the product to be delivered directly to approved prescribers (predominantly GPs), who will administer doses to patients within the practice. This is a significant shift away from the current model which is predominantly delivered through community pharmacy. The capacity of GPs to deliver this service is unclear.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of buprenorphine, in the form prolonged release injection, for treatment of patients with opiate dependence, on the basis that the claim of superior comparative effectiveness was not adequately supported by the evidence provided, and therefore that the request for a higher price for this treatment compared to existing treatments for opiate dependence was not justified.
- 7.2 The PBAC acknowledged that there may be additional benefits of treatment with prolonged buprenorphine compared to existing treatments for some patients, including that private fees charged to patients may be lower due to reduced frequency of administration, and noted that some of these benefits cannot be accurately quantified. Acknowledging the changing demographics of opioid misuse, with increasing misuse of prescription opioids in place of illicit opioids, the PBAC agreed that there is a clinical place for a treatment that is administered through a model that is predominantly general practice based, particularly for patients who currently choose not to be treated under the existing pharmacy-based model.
- 7.3 The PBAC accepted sublingual buprenorphine/naloxone was an appropriate comparator, and agreed that any opioid substitution therapy including methadone or sublingual buprenorphine may be replaced by prolonged release buprenorphine as there are no significant differences in the populations currently accessing the range of treatment options.
- 7.4 The PBAC considered that the results of trial HS-11-421 showed no significant difference in efficacy compared to sublingual buprenorphine/naloxone in terms of percentage urine samples negative for illicit opioids (with and without self-reported illicit opioid use), proportion of patients abstaining from opioid use, or percentage of patients remaining on treatment.

- 7.5 The PBAC agreed with ESC that despite a statistically significant benefit of prolonged release buprenorphine over sublingual buprenorphine/naloxone demonstrated for the cumulative distribution function of proportion of negative urine samples, the measure was difficult to interpret and was of unclear clinical significance, and was therefore not sufficient to support the claim of superior efficacy given all other clinical measures demonstrated non-inferiority. As such, the PBAC was not satisfied that prolonged release buprenorphine demonstrated superior comparative effectiveness over sublingual buprenorphine/naloxone, and agreed with the ESC that a claim non-inferior comparative efficacy was more reasonable.
- 7.6 The PBAC accepted the claim of non-inferior comparative safety to sublingual buprenorphine/naloxone.
- 7.7 As the claim of superior comparative effectiveness was not supported, the PBAC did not accept the economic analysis presented in the submission nor the revised base case economic model presented in the pre-PBAC response.
- 7.8 Based on the accepted clinical claim of non-inferior efficacy and safety, the PBAC considered a cost-minimisation analysis compared to sublingual buprenorphine/naloxone would be more appropriate. The PBAC considered that a modest price premium may be acceptable in acknowledgement of the unquantifiable benefits of a new treatment option that is administered in a different treatment setting and is likely utilised by a population who currently choose not to be treated.
- 7.9 The PBAC agreed with DUSC that utilisation of prolonged release buprenorphine, and the likely substitution from other opioid substitution therapies, cannot be reliably determined until the practice model is known, such as whether the product will be supplied through a patient's usual dispensing site (including community pharmacy) or whether access will be limited to use in alcohol and drug treatment clinics, public or private health clinics, or through general practice. Similarly, health system costs including the costs of administration and GP visits are reliant on the practice model adopted and therefore cannot be reliably estimated.
- 7.10 The PBAC agreed that there is potential for market growth to occur as a result of listing prolonged release buprenorphine, as there are currently patients who choose not to be treated for opioid use disorder under the current pharmacy-based model. Due to the convenience of monthly injections and potential for increased social acceptability of a practice model delivered through general practice, it is likely that patients not currently receiving any opioid substitution therapy will initiate treatment with prolonged release buprenorphine. This population was not captured in the market share approach.
- 7.11 The PBAC considered that any future listing of prolonged release buprenorphine should be implemented under the existing Section 100 Opioid Dependence Treatment Program (ODTP), noting the supply of the drug would be restricted to approved prescribers who would also administer the dose. However, it agreed with

DUSC that this is a significant shift away from the current community pharmacy based model, and the capacity of medical practitioners to manage this, and associated costs, is unclear. The PBAC further noted that implementation of any future positive recommendation would require significant liaison with states and territories.

7.12 The PBAC considered that a minor resubmission would be suitable based on a clinical claim of non-inferiority, a cost minimisation analysis to sublingual buprenorphine/naloxone based on an equivalent cost per day, and updated costs associated with a GP-based Section 100 implementation model. However, if a superiority claim and associated cost-effectiveness analysis is maintained, a major resubmission would be required to justify the approach, with changes to the economic model aligned with the ESC revised base case.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

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

Camurus refers to the published scientific data regarding the comparative effectiveness of the prolonged buprenorphine injection and daily sublingual buprenorphine/naloxone. Camurus is convinced of the benefit of prolonged release buprenorphine in this patient group with a demonstrated clinically meaningful change in illicit drug use behaviour shown by superiority on the cumulative distribution function and non-inferiority on the responder rate and will continue to seek PBS reimbursement based on the advice from PBAC.