

5.02 BUPRENORPHINE,

Injection (modified release) 100 mg in 0.5 mL pre-filled syringe

Injection (modified release) 300 mg in 1.5 mL pre-filled syringe

Sublocade[®], Indivior Pty Ltd

1 Purpose of Application

- 1.1. The submission sought a Section 100 (Opiate Dependence Treatment Program) listing for buprenorphine long-acting subcutaneous injection (Sublocade[®]) for treatment of opioid use disorder. This was the first submission to the PBAC for Sublocade.
- 1.2. The submission's requested basis for listing was a cost-minimisation analysis with a price premium, based on a claim of non-inferiority in terms of efficacy and adverse events and superiority in terms of harm reduction. The submission also included a supplemental cost-effectiveness analysis as additional support for the price premium.
- 1.3. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Patients with opioid use disorder
Intervention	Buprenorphine long-acting injection (Sublocade [™])
Comparator	Primary comparator: BUP/NAL SL film (Suboxone [®]) Near market comparator: Buprenorphine long-acting subcutaneous injection (Buvidal [®])
Outcomes	Percentage abstinence (composite primary outcome from urine samples and self-report) treatment success defined as ≥80% urine samples negative for opioids combined with self-report; TEAEs and other serious AEs
Clinical claim	In patients with opioid use disorder, Sublocade is: <ul style="list-style-type: none"> • Non-inferior to BUP/NAL SL film in terms of efficacy, and superior in terms of harm reduction • Non-inferior to Buvidal in clinical outcomes (efficacy and safety)

Source: Table 1.1, p21 of the submission.

AE = adverse event; TEAE = treatment-emergent adverse event;

2 Requested listing

- 2.1. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – March 2019 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Max. Qty	Price for	Proprietary Name and Manufacturer
BUPRENORPHINE Solution for subcutaneous injection 100mg Solution for subcutaneous injection 300mg	1	0	\$ [REDACTED]		Sublocade Indivior Pty Ltd

Category / Program	Section 100 – Opiate Dependence Treatment Program
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
Episodicity:	-
Severity:	-
Condition:	Opiate dependence
PBS Indication:	Opiate dependence
Treatment phase:	Initial and continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	The treatment must be within a framework of medical, social and psychological treatment <i>AND</i> <i>The treatment must be administered by a health care professional.</i>
Population criteria:	N/A
Foreword	N/A
Definitions	N/A
Prescriber Instructions	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.
Administrative Advice	Care must be taken to comply with the provisions of State/Territory law when prescribing this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
Cautions	

- 2.2. Prices are listed at the ex-manufacturer level as under the Opioid Dependence Treatment Program arrangements, the Commonwealth funds the full cost of the medicine via direct payment to the drug sponsors.
- 2.3. The proposed Section 100 listing is consistent with existing Section 100 (Opiate Dependence) listings.
- 2.4. The requested restriction did not indicate that Sublocade treatment should be initiated after stabilisation of withdrawal symptoms on a buprenorphine-containing product. This was inconsistent with the trial evidence and the Draft PI for Sublocade. The ESC agreed that it would be appropriate for the restriction to specify that treatment must be administered by a health care professional, consistent with the Draft PI for Sublocade. Direct administration by a health professional (medical practitioner or nurse practitioner) will be a significant shift away from the current community pharmacy-based practice model.
- 2.5. The submission specified Sublocade is anticipated to be provided by:
 - Public and private clinics that order from wholesalers.
 - Corrective service / Justice Health medical services who directly order through wholesalers.
 - A limited number of pharmacies that employ a nurse or enter into shared care arrangements with local health authorities.
 - Medical practices with low volume of patients who make individual arrangements with pharmacies to deliver to their medical practice.
 - Medical practices co-located with pharmacies who will deliver to prescribers.
 - Medical / Nursing Practices with high volume of patients who may directly order (subject to state/territory approval) from a wholesaler.
 - Market forces may lead to additional models developing.
- 2.6. The proposed indication and restriction for Sublocade was opiate dependence. Whilst this is consistent with the PBS indication for BUP/NAL SL, it may be a narrower definition than the DSM-5 diagnostic criteria used in the RB-US-13-0001 trial (the main source of evidence for Sublocade in the submission). The main difference between DSM-5 and DSM-4 is that DSM-5 effectively combined DSM-4 diagnoses of opioid dependence and opioid abuse¹.
- 2.7. 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.

¹ Center for Behavioral Health Statistics and Quality. (2016). Impact of the DSM-IV to DSM-5 Changes on the National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration, Rockville, MD

Time for liaison with states and territories would need to be factored into implementation of a positive recommendation for this product.

- 2.8. The submission noted that the sponsor wrote to State and Territory Health Ministers seeking discussions on the appropriate policy regulatory framework to ensure patients would not handle Sublocade. This was followed in several states with briefings.
- 2.9. The submission also noted that the sponsor will seek written agreement that the relevant health professional is aware and agrees to ensure that a patient will not possess or handle Sublocade.

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

3 Background

Registration status

- 3.1. The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA clinical evaluator's report (first round) became available. The TGA first round Clinical evaluator concluded that the risk-benefit balance for Sublocade was favourable. The TGA Delegate's Overview was expected to be received on 7 May 2019, following PBAC consideration.
- 3.2. The proposed TGA indication is the treatment of opioid dependence, within a framework of medical, social and psychological treatment.

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

4 Population and disease

- 4.1. Opioid use disorder (OUD) is a chronic, relapsing condition that is characterised by compulsive administration of opioid substances for non-medical uses or administration in excessive doses (American Psychiatric Association, 2013).
- 4.2. Opioid use and misuse may result in dependence, overdose, physical harm or death. The submission cited AIHW (2018) data that described opioid use as responsible for 0.9% of the total burden of disease and injuries, with most of the burden of opioid use due to accidental poisoning (63%) and opioid dependence (29%). A further 7.8% was due to suicide and self-inflicted injuries.
- 4.3. The submission cited a study by Degenhardt et al 2014, which found that Australia has among the highest estimated prevalence of opioid dependence (0.46%) along with the United Kingdom (0.48%) and New Zealand (0.46%).
- 4.4. Sublocade is recommended for use after initial treatment of withdrawal symptoms with buprenorphine or BUP/NAL. The ESC considered that it was most likely that in Australian clinical practice, patients would be stabilised on daily BUP/NAL SL film and be responding well to treatment, including being authorised for multiple takeaway doses. It was likely at that point, patients might be considered to be good candidates for transitioning to a long-acting injectable formulation. As such, the ESC considered that Sublocade would be used later in the treatment algorithm.

4.5. Sublocade is provided in dosage strengths of 100mg and 300mg. The recommended dose of Sublocade is 300mg monthly for the first two months, followed by a maintenance dose of 100mg monthly. The submission noted that patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300mg monthly. Buprenorphine plasma levels in the month following the second 300mg dose are maintained with 100mg maintenance dosing. The 300 mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection.

4.6. Treatment with Sublocade is expected to continue indefinitely.

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

5 Comparator

5.1. The submission nominated BUP/NAL SL film as the main comparator. The main argument provided in support of this nomination was that this was the medicine most likely to be replaced in practice, with a 'minute proportion of buprenorphine and methadone use shifting to Sublocade'.

5.2. The submission considered BUP/NAL SL film was the medicine most likely to be replaced based on the NOPSAD 2017 snapshot days in May 2017 and June 2017 of clients receiving opioid pharmacotherapy treatment, doctors prescribing opioid pharmacotherapy drugs, and the dosing points that clients attend to receive their medication (AIHW 2018). The ESC agreed that BUP/NAL SL film was the appropriate main comparator.

5.3. The submission noted that 40% of all clients receiving opioid dependence treatment (ODT) were prescribed buprenorphine or BUP/NAL, with BUP/NAL identified in guidelines as a preferred treatment due to the reduced potential for diversion (Gowling 2014).

5.4. The submission considered that trends in prescribing and utilisation of ODT have shown a reduction in use of methadone, replaced by BUP/NAL SL film. The submission also noted that methadone patients are typically older, have been accessing ODT maintenance in the form of methadone for a longer period, and display a great reluctance to change their ODT. Buprenorphine and BUP/NAL are more likely to be prescribed in younger cohorts. The submission also noted that methadone induction is now uncommon compared to BUP/NAL SL film induction. The submission considered that due to this assessment, current methadone patients will largely continue methadone maintenance therapy, and not access Sublocade. The ESC agreed that while methadone could also be an appropriate comparator in some patients, it was less likely to be replaced by Sublocade.

5.5. For the requested population, the alternative therapies listed on the PBS (methadone, buprenorphine, and BUP/NAL) are less costly than the requested price for Sublocade. If treatment with Sublocade is substantially more costly than an alternative therapy or alternative therapies, the PBAC can only recommend listing of Sublocade if it is satisfied that Sublocade provides, for some patients, a significant improvement in

efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953*, Section 101(3B)).

- 5.6. The submission also noted that buprenorphine long-acting subcutaneous injection (herein referred to as Buvidal®) was on the agenda for the November 2018 PBAC meeting, and thus considered a ‘near market comparator.’ After lodging the Sublocade submission, the PBAC outcomes for Buvidal became available. Buvidal did not receive a positive recommendation for listing. A minor resubmission for Buvidal was considered at the March 2019 PBAC meeting.

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 sponsor presented information regarding the social impacts of opioid dependence, and highlighted key results of the clinical evidence presented in the submission. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

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 the following trials:
- RB-US-13-0001 (n=504), a randomised double-blind trial comparing Sublocade to placebo over 24 weeks in multiple centres in the USA;
 - Rosenthal (2013; n=287), a randomised double-blind trial comparing four buprenorphine implants, four placebo implants and open-label BUP/NAL SL tablet in multiple centres in the USA; and
 - Lofwall (2018; n=428), a randomised double-blind trial comparing BUP/NAL SL tablets versus Buvidal at multiple centres in the United States.
- 6.4. The submission also included discussion of three long-term safety studies: RB-US-13-0003; INDV-6000-301 and RECOVER.
- 6.5. Details of the trials and long-term safety studies are presented in the submission are provided in Table 2.

Table 2: Trials and associated reported presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised controlled trials		
RB-US-13-0001 (NCT02357901)	Clinical Study Report RB-US-13-0001: A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (RBP-6000 [100 mg and 300 mg]) over 24 weeks in treatment-seeking subjects with opioid use disorder.	03 March 2017
	Laffont C, Ngaimisi E, Gopalakrishnan M, et al. Predictors of retention in treatment for opioid use disorder following administration of RBP-6000 vs. Placebo.	28th Annual Meeting and Symposium of the American Academy of Addiction Psychiatry, AAAP 2017. United States. 2018;27(4):328.
	Haight B, Andorn A, Laffont C, et al. RBP-6000 buprenorphine monthly depot demonstrates sustained clinical efficacy and safety in phase III opioid use disorder trials.	Conference: 56th Annual Meeting of the American College of Neuropsychopharmacology, ACNP 2017. United States. 2017;43(Supplement 1):S463-S464.
	Nadipelli VR, Solem CT, Ronquest NA, et al. Impact of RBP-6000 on Patient-reported Outcomes in Patients with Opioid Use Disorder: Results of a Randomized, Placebo-controlled, Phase 3 Study.	The 41st Association of Medical Education and Research in Substance Abuse (AMERSA) Annual National Conference, Washington, D.C., November 2 - 4, 2017.
Rosenthal 2013	Rosenthal RN, Ling W, Casadonte P, et al. Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone	Addiction. 2013;108(12):2141-2149.
Lofwall 2018 (NCT02651584)	Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder a randomized clinical trial.	JAMA Internal Medicine. 2018;178(6):764-773.
	Clinical Trial Protocol HS-11-421: A phase III, randomized, double-blind, active-controlled, parallel group, multi-center 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.	V 6.0. 03 November 2016.
	Lofwall M, Nunes EV, Bailey GL, et al. Efficacy of buprenorphine (BUP) depot injections vs. sublingual BUP for opioid use disorder: A phase 3 RCT.	Conference: 28th Annual Meeting and Symposium of the American Academy of Addiction Psychiatry, AAAP 2017. United States. 2018;27(4):282-283.
	FDA Advisory Committee meeting briefing document CAM2038 (buprenorphine) subcutaneous injection	01 November 2017.
Long term studies		
RB-US-13-0003 (NCT02510014)	Clinical Study Report RB-US-13-0003: An open-label, long-term safety and tolerability study of depot buprenorphine (RBP-6000) in treatment-seeking subjects with opioid use disorder.	16 January 2018.
	Ling W, Nadipelli VR, Solem CT, et al. Impact of RBP-6000 (Once-Monthly Depot Buprenorphine) on Patient-Reported Outcomes: A Long-Term Study.	The American Society of Addiction Medicine 49th Annual Conference, San Diego, April 12-15, 2018.

Trial ID	Protocol title/ Publication title	Publication citation
INDV-6000-301 (NCT02896296)	Clinical Study Report INDV-6000-301: An open-label, depot buprenorphine (RBP-6000) treatment extension study in subjects with opioid use disorder.	12 March 2018.
RECOVER (NCT03604861)	Remission from Chronic Opioid Use - Studying Environmental and Socio-economic Factors on Recovery (RECOVER): 12-Month Preliminary Outcomes Following RBP-6000 Phase III Study Participants.	15 October 2018.

Source: Tables 2.5, p52, 2.6, p53 and 2.10, p57 of the submission.

6.6. The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Sublocade versus Placebo						
RB-US-13-0001	504	R, DB 24 weeks*	Low	DSM 5 opioid use disorder	Self-reported opioid use and negative UDS; completers	NA
BUP /NAL SL tablet versus placebo injections						
Rosenthal 2013	287	R, OL** 24 weeks*	High	DSM 4 opioid dependence	Negative UDS; completers	NA
Buvidal versus BUP /NAL SL tablet						
Lofwall (2018)	428	R, DB 24 weeks*	Low	DSM 5 opioid disorder	Self-reported opioid use and negative UDS; completers	NA

DB=double blind; MC=multi-centre; NA = not applicable; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; UDS = urine drug screen

Source: compiled during the evaluation

* all trials had a 24 week treatment phase

** the relevant treatment arm, BUP/NAL SL tablets, was open-label. Other treatment arms (placebo and buprenorphine implants were double-blind.

Comparative effectiveness

6.7. Table 4 presents key results from the RB-US-13-0001 trial.

Table 4: Key results of RB-US-13-0001

Endpoint	Placebo	Sublocade 300 mg/100 mg		Sublocade 300 mg/300 mg	
	N = 99	N = 194	P-Value*	N = 196	P-Value*
CDF of percentage abstinence weeks 5-24 FAS, mean (SD)	5.0% (16.98%)	42.7% (38.50%)	<0.0001	41.3% (39.66%)	<0.0001
CDF urine samples negative, mean (SD)	7.0% (19.34%)	46.0% (39.58%)	<0.0001	43.8% (40.24%)	<0.0001
CDF self-reports negative illicit opioid use, mean (SD)	19.1% (31.41%)	63.0% (38.59%)	<0.0001	62.1% (39.56%)	<0.0001
Subjects abstinent at week 24, n (%)	2 (2.0)	71 (36.6)	<0.0001	87 (44.4)	<0.0001
Treatment success,** n (%)	2 (2.0)	55 (28.4)	<0.0001	57 (29.1)	<0.0001
Subjects who are completers, n(%)	33 (33.3)	119 (61.3)	<0.0001	126 (64.3)	<0.0001

Source: Table 2.46, p91, Table 2.47, p 94, Table 2.49, p96, Table 2.50, p 96, Table 2.51, p97, Table 2.52, p97 of the submission.

CDF = cumulative distribution function; FAS = full analysis set; IDC = individual drug counselling; mg = milligram.

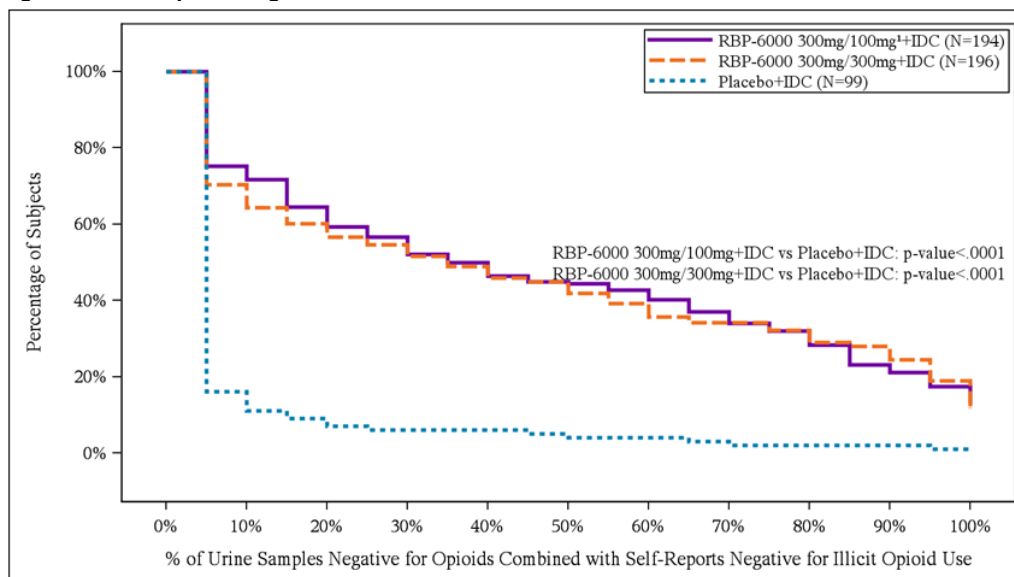
Note: all treatment groups included IDC

* versus placebo

** treatment success was defined as any subject with ≥80% urine samples negative for opioids combined with self -reports negative for illicit opioid use between Weeks 5 and 24

6.8. Figure 1 presents the results of the primary efficacy endpoint for the RB-US-13-001 trial: cumulative distribution function (CDF) of percentage abstinence, weeks 5-24.

Figure 1: CDF of percentage abstinence, Weeks 5-24 FAS in RB-US-13-001



Source: Figure 2.6, p92 of the submission.

CDF = cumulative distribution function; FAS = full analysis set; IDC = individual drug counselling; mg = milligram;

Note: 300mg/100mg mean (SD): 42.7% (38.50%); 300mg/400mg mean (SD): 41.3% (39.66%); Placebo mean (SD): 5.0% (16.9%)

6.9. The results indicated that both Sublocade groups (300mg initiation followed by 100mg/month or 300mg/month) were associated with statistically significant improvements in percentage abstinence by CDF compared to placebo.

6.10. Overall the evidence, suggests that Sublocade is more effective than placebo. The TGA first round Clinical Evaluator concluded that the risk-benefit balance for Sublocade was favourable.

6.11. Table 5 presents key results of the Rosenthal (2013) trial.

Table 5: Key results of Rosenthal (2013) trial

Endpoint	Placebo implants	Buprenorphine implants		BUP/NAL SL tablets	
	N = 54	N = 114	P-Value*	N = 119	P-Value**
CDF urine samples negative, mean (95% CI) without imputation based on self-report	13.4% (8.3, 18.6)	31.2% (25.3, 37.1)	NR	33.5% (27.3, 39.6)	NR
CDF urine samples negative, mean (95% CI) with imputation based on self-report	12.8% (7.1, 17.9)	31.0% (25.1, 36.8)	NR	33.1% (27.0, 39.2)	NR
Proportion of urine samples negative, weeks 1-24, mean	14.4%	36.0%	<0.0001	35.1%	0.81
Proportion of urine samples negative weeks 1-16, mean	17.9%	39.6%	<0.0001	37.8%	0.65
Proportion of urine samples negative weeks 17-24, mean	7.2%	28.9%	<0.0001	29.6%	0.86
Subjects who completed treatment, n(%)	14 (25.9%)	73 (64.0%)	<0.0001	76 (63.9%)	0.62

Source: Table 2.58 Table 2.59, and Table 2.60, p109, the submission.

CDF = cumulative distribution function; CI = confidence interval; FAS = full analysis set; IDC = individual drug counselling; mg = milligram.

Note: all treatment groups included IDC

* versus placebo

** buprenorphine implants vs BUP/NAL SL tablets

6.12. Overall, as no statistical comparison was made between placebo and BUP/NAL SL tablet, the individual trial results are not informative.

6.13. The ESC noted the significant difference in the placebo response rate between the RB-US-0001 and Rosenthal trials raised transitivity concerns. The significance of this difference on the results of the indirect comparison, particularly given the lack of reported baseline characteristics to determine comparability between trials, was unknown.

6.14. Table 6 presents the results of the indirect comparison between Sublocade and BUP/NAL SL tablet.

Table 6: Results of indirect comparison of Sublocade versus sublingual buprenorphine / naloxone

Outcome	RD(95% CI)	SE (ln RD)*	P value (non-inferiority)
Sublocade 300/100mg versus BUP/NAL via placebo			
CDF % abstinent (mean difference)	0.176 (0.027, 0.325)	0.076	0.020
Urine sample negative	0.183 (0.029, 0.337)	0.078	0.019
Completers at week 24	-0.099 (-0.285, 0.086)	0.095	0.294
Sublocade 300/300mg versus BUP/NAL via placebo			
CDF % abstinent (mean difference)	0.162 (0.14, 0.310)	0.076	0.032
Urine sample negative	0.161 (0.008, 0.314)	0.078	0.039
Completers at week 24	-0.070 (-0.255, 0.115)	0.094	0.459

Source: Table 2.77, and Table 2.78, pp131-132 of the submission.

CDF = cumulative distribution function; CI = confidence interval; mg – milligram; RD = risk difference; SE = standard error TEAE = treatment emergent adverse event; **Bold** indicated statistically significant result

* the submission did not define the abbreviation 'ln' – presumably natural log. Further details of the standard error calculation were not presented.

6.15. For the indirect comparison, the submission selected a 15% non-inferiority margin for CDF (Rosenthal 2018), 11% margin for mean proportion of opioid negative urine samples for 24 weeks (Lofwall 2018), and 15% margin for study retention (Lofwall 2018).

- 6.16. The ESC noted that the outcomes of CDF percentage abstinent and urine sample negative met the nominated non-inferiority margins and achieved statistical significance; however, the lower 95% confidence interval for the difference in completers at 24 weeks exceeded the nominated non-inferiority margin of 15% for both the Sublocade 300/100mg and the 300/300mg doses suggesting possible inferiority.
- 6.17. Overall, the nominated margins were considered to be not informative as the indirect comparison was likely invalid due to significant differences in the Rosenthal (2013) and RB-US-13-0001 trials which limited exchangeability, specifically:
- The open label nature of the BUP/NAL SL arm of Rosenthal (2013). The Pre-Sub-Committee Response (PSCR) suggested that the open label nature of the Rosenthal trial was biased against Sublocade and was therefore appropriate. However, the ESC agreed that the open label design of the Rosenthal trial may limit the comparability of trials for the purposes of an indirect comparison.
 - The potential sub-optimal dosing of BUP/ NAL SL arm of Rosenthal (2013). The submission considered that mean dosing of Rosenthal (2013) was lower than what would be expected in the Australian treatment population. If this is accurate, BUP/NAL SL tablets may have been administered at sub-therapeutic doses, and doses lower than could be expected in other trials or in the Australian population. The PSCR considered that the dose was adequate, not sub-therapeutic, and that patients in the Rosenthal trial represented an easier to treat population. The ESC considered that this further highlighted the exchangeability issues in the indirect comparison.
 - The lack of information on important baseline characteristics of the Rosenthal (2013) trial with regards to non-pharmacological predictors of treatment success (including but not limited to, marital status, housing status, employment status, education, severity of disease). The PSCR noted recent evidence which found that only age and housing were found to have an effect on treatment success, and the ESC therefore considered that the trial results are likely reflective of the Australian context.
- 6.18. Overall, while the submission's analysis suggests non-inferiority of the selected outcomes, due to critical differences in the trials lack of information in many important baseline characteristics, little confidence can be placed on the results of the indirect comparison of Sublocade to BUP/NAL SL film. The ESC agreed that due to exchangeability issues with the clinical evidence, it remained challenging to draw conclusions about the non-inferiority claim.
- 6.19. Table 7 presents the results of the indirect comparison between Sublocade and Bupivacaine.

Table 7: Results of indirect comparison of Sublocade versus Bupivacaine

Outcome	RD (95% CI)	SE (ln RD)*	P value
Sublocade 300/100mg versus Bupivacaine via placebo and BUP/NAL			
CDF % abstinent (mean difference)	0.092 ((-0.080, 0.264))	0.088	0.296
Urine sample negative	0.116 (-0.061, 0.293)	0.090	0.199
Completers at week 24	-0.064 (-0.268, 0.141)	0.104	0.540
Sublocade 300/300mg versus Bupivacaine via placebo and BUP/NAL			
CDF % abstinent (mean difference)	0.078 (-0.094, 0.250)	0.088	0.375
Urine sample negative	0.094 (-0.083, 0.271)	0.090	0.297
Completers at week 24	-0.034 (-0.239, 0.170)	0.104	0.741

Source: Table 2.79, and Table 2.80, pp132-133 of the submission.

CDF = cumulative distribution function; CI = confidence interval; mg = milligram; RD = risk difference; SE = standard error TEAE = treatment emergent adverse event

* the submission did not define the abbreviation 'ln' – presumably natural log. Further details of the standard error calculation were not presented.

6.20. The ESC noted that while the outcomes of CDF percentage abstinent and urine sample negative were within the nominated non-inferiority margin, the lower bound of the 95% confidence interval for the outcome of completers at 24 weeks exceeded the nominated 15% non-inferiority margin. However, as this comparison was made via two common comparators (placebo and BUP/NAL SL of the Rosenthal 2013 trial), all of the issues affecting the comparison of Sublocade and BUP/NAL SL also affected this comparison. The ESC agreed that overall, the results of this comparison were not reliable.

Comparative harms

6.21. Table 8 presents a summary of the safety results of RB-US-13-0001.

Table 8: Summary of safety results for RB-US-13-0001

Endpoint	Placebo	Sublocade 300 mg/100 mg	P-Value*	Sublocade 300 mg/300 mg	P-Value
	N = 100	N = 203		N = 201	
Any TEAE	56 (56.0)	155 (76.4)	0.11	134 (66.7)	0.38
Study Treatment-Related TEAEs (per investigator)	23 (23.0)	67 (33.0)	0.18	70 (34.8)	0.12
Serious TEAEs	5 (5.0)	4 (2.0)	0.15	7 (3.5)	0.37
Serious Study Treatment-Related TEAEs (per investigator)	0 (0.0)	0 (0.0)	1.0	0 (0.0)	1.0
Death	0 (0.0)	0 (0.0)	1.0	1 (0.5)	1.0
Severe TEAEs	4 (4.0)	15 (7.4)	0.28	13 (6.5)	0.29
TEAEs Leading to Study Treatment Discontinuation	2 (2.0)	7 (3.4)	0.39	10 (5.0)	0.19
Headache	6 (6.0)	19 (9.4)	0.35	17 (8.5)	0.48
Constipation	0 (0.0)	19 (9.4)	0.0007	16 (8.0)	0.0019
Nausea	5 (5.0)	18 (8.9)	0.19	16 (8.0)	0.37
Injection site pruritus	4 (4.0)	13 (6.4)	0.30	19 (9.5)	0.01
Vomiting	4 (4.0)	19 (9.4)	0.09	11 (5.5)	0.41
Insomnia	11 (11.0)	13 (6.4)	0.20	17 (8.5)	0.52
Upper respiratory tract infection	1 (1.0)	15 (7.4)	0.017	12 (6.0)	0.043
Injection site pain	3 (3.0)	10 (4.9)	0.34	12 (6.0)	0.22
Nasopharyngitis	1 (1.0)	11 (5.4)	0.06	10 (5.0)	0.08
Fatigue	3 (3.0)	8 (3.9)	0.49	12 (6.0)	0.22
Anxiety	5 (5.0)	10 (4.9)	0.59	8 (4.0)	0.70
Drug withdrawal syndrome	6 (6.0)	9 (4.4)	0.57	7 (3.5)	0.33
Blood creatine phosphokinase increased	1 (1.0)	11 (5.4)	0.06	5 (2.5)	0.36
Diarrhoea	5 (5.0)	5 (2.5)	0.21	5 (2.5)	0.27

Source: Table 2.65, p117 and Table 2.66, p118 of the submission.

- 6.22. Overall, compared to placebo, both doses of Sublocade had statistically significantly higher proportions of patients with constipation and upper respiratory tract infections.
- 6.23. There did not appear to be any discernible patterns in serious treatment emergent adverse events (TEAE) between the treatment groups.
- 6.24. As evidenced by FDA boxed warning against intravascular injection, and the consistent concern for tampering with the depot in the Sublocade trial program, there remains a risk (though no instances have been recorded) of attempts to tamper with and remove the depot. It would be expected that should Sublocade be made available to more patients, cases will occur. Secondly, the potential harms associated with misuse of Sublocade are serious - injury or death.
- 6.25. Table 9 presents the safety results of the submission's indirect comparison.

Table 9: Results of indirect comparison of Sublocade versus sublingual BUP/NAL

Outcome	RD(95% CI)	SE (ln RD)*	P value
Sublocade 300/100mg versus BUP/NAL via placebo			
Any TEAEs	1.00 (-0.090, 0.291)	0.097	0.302
Serious TEAEs (both fatal and non-fatal)	-0.034 (-0.121, 0.054)	0.045	0.454
Sublocade 300/300mg versus BUP/NAL via placebo			
Any TEAEs	0.003 (-0.189, 0.196)	0.098	0.972
Serious TEAEs (both fatal and non-fatal)	-0.018 (-0.108, 0.071)	0.046	0.686

Source: Table 2.77, and Table 2.78, pp131-132 of the submission.

CDF = cumulative distribution function; CI = confidence interval; mg = milligram; RD = risk difference; SE = standard error TEAE = treatment emergent adverse event

* the submission did not define the abbreviation 'ln' – presumably natural log. Further details of the standard error calculation were not presented.

6.26. Table 10 presents the indirect safety comparison of Sublocade versus Bupival presented in the submission.

Table 10: Results of indirect comparison of Sublocade versus Bupival

Outcome	RD(95% CI)	SE (ln RD)*	P value
Sublocade 300/100mg versus Bupival via placebo and BUP/NAL			
Any TEAEs	0.053 (-0.159, 0.265)	0.108	0.625
Serious TEAEs (both fatal and non-fatal)	-0.001 (-0.097, 0.095)	0.049	0.979
Sublocade 300/300mg versus Bupival via placebo and BUP/NAL			
Any TEAEs	-0.044 (-0.258, 0.170)	0.109	0.688
Serious TEAEs (both fatal and non-fatal)	0.014 (-0.084, 0.111)	0.050	0.781

Source: Table 2.79, and Table 2.80, pp132-133 of the submission.

CDF = cumulative distribution function; CI = confidence interval; mg = milligram; RD = risk difference; SE = standard error TEAE = treatment emergent adverse event

* the submission did not define the abbreviation 'ln' – presumably natural log. Further details of the standard error calculation were not presented.

Clinical claim

6.27. The submission described Sublocade as non-inferior in efficacy compared to BUP/NAL SL film, and non-inferior in safety compared to BUP/NAL SL film in terms of treatment emergent adverse events. The submission further described Sublocade as superior to BUP/NAL SL film in terms of harm reduction based on an assumption of 0% misuse of Sublocade and estimates of diversion, and injection of diverted doses of BUP/NAL SL film from Larance (2016).

6.28. The outcomes on which the submission based the claim of non-inferior efficacy were:

- cumulative distribution function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use;
- proportion of urine samples negative; and
- proportion of completers at week 24.

6.29. The level of evidence presented to support the claim of non-inferior efficacy was likely insufficient to support the submission's claim, as outlined in paragraph 6.17. The ESC considered that the substantive limitations in the indirect comparison made it challenging to accept the non-inferiority claim, however on balance considered that this was likely to be reasonable.

- 6.30. The submission's claim of non-inferior safety had the same evidentiary problems as the efficacy claim. However, non-inferior safety in terms of treatment emergent adverse events was generally supported by the trial evidence and indirect comparison with the exception of injection site reactions. The ESC considered that the claim of non-inferior safety was reasonable, noting that the nature of the differing formulations means that injection site reactions will be greater for Sublocade.
- 6.31. Whilst it was conceivable that benefits in harm reduction in terms of reduced diversion 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. Several issues were identified with the submission's claim of superior safety in terms of harm reduction, as follows:
- The harm reduction superiority claim was predicated on the acceptance of non-inferior efficacy and adverse events, which may not be accepted.
 - While Larance (2016) indicates a small but existent proportion of patients injecting BUP/NAL SL film (in 2012 and 2013), the submission makes several assumptions regarding diversion in the Australian treatment landscape should Sublocade be listed. Firstly, as indicated by the FDA boxed warning against intravascular injection, and the consistent concern for tampering with the depot in the Sublocade trial program, there remains a risk (though no instances have been recorded) of attempts to tamper with and remove the depot. It would be expected that should Sublocade be made available to more patients, such diversion could occur. Secondly, the potential harms associated with misuse of Sublocade are serious - injury or death, which means that even a small proportion of patients misusing Sublocade could invert the submissions' claim of superiority in harm reduction.
 - The submission did not adequately address the benefits for some patients of receiving BUP/NAL daily, particularly in accessing professional care daily, and reinforcing treatment goals. While the submission stressed that injection with Sublocade is completely supervised, patients potentially remain unsupervised or unmonitored for an entire month. There are likely to be some patients who may have an improved therapeutic response to opioid substitution therapies because of more regular interaction with a healthcare provider.
 - The ESC considered the rate of diversion with the BUP/NAL SL film is likely to be overestimated, as the patients most likely to access Sublocade are patients stabilised on BUP/NAL SL film and responding well to treatment. These are likely to be existing patients not misusing treatment and therefore unlikely to be diverting. Consequently, the extent of further reduction in the rate of misuse is likely to be overestimated. The patients most likely to divert or misuse treatment may elect to stay on BUP/NAL SL film, rather than go on Sublocade.
 - Lastly, even if a small proportion of diverted doses of BUP/NAL SL film were avoided due to listing of Sublocade, no estimation of how this would translate to mortality or health-related quality of life was presented. The ESC considered that this was

essential to determining the incremental cost-effectiveness of Sublocade over existing treatments.

- 6.32. Overall, should the non-inferior efficacy of Sublocade be accepted, it would potentially have a useful place in the Australian treatment setting for some patients. However, the advantages appear to have been overstated. The ESC considered that the claim of superiority in terms of harm reduction was highly uncertain, and that the size of any such benefit is unknown.
- 6.33. The submission also described Sublocade as demonstrating non-inferiority in terms of efficacy and safety against Buprenorphine in patients with opioid use disorder. The ESC considered that the claim was unreliable based on the evidence provided in the submission, but that it was not unreasonable that the two products would provide similar clinical benefits.
- 6.34. The PBAC considered that the claim of non-inferior comparative effectiveness compared to BUP/NAL SL film was reasonable.
- 6.35. The PBAC considered that the claim of non-inferior comparative safety compared to BUP/NAL SL film in terms of treatment emergent adverse events was reasonable. While the PBAC acknowledged that there may be additional benefits associated with treatment with a long acting injectable form of buprenorphine, including a reduced risk of diversion, it considered that the claim of superiority in terms of harm reduction was not adequately supported by the data presented in the submission.

Economic analysis

- 6.36. The submission presented a cost-minimisation analysis against BUP/NAL based on the clinical claim of non-inferior efficacy and adverse events.
- 6.37. The proposed equi-effective doses were:
 - Sublocade 300mg monthly and Sublocade 100mg monthly was equivalent to BUP/NAL SL film 19.6 mg daily; and
 - Sublocade 300mg monthly and Sublocade 100mg monthly was equivalent to Buprenorphine 110.7mg monthly.
- 6.38. The submission stated that a steady state dose cannot be determined in Rosenthal (2013) due to the protocol defined dosing and the use of rescue BUP/NAL SL tablets. The submission noted that the authors considered the use of rescue BUP/NAL SL tablets across all groups. Though it appeared that no patients in the BUP/NAL SL tablet arm used rescue BUP/NAL SL tablets, it appeared that the dosing may have been sub-optimal.
- 6.39. However, as the claim of non-inferior efficacy was based on this dosage from Rosenthal 2013, it was inappropriate that the higher dosage used in Lofwall was used as the basis of the equi-effective dose calculation for the cost-minimisation.
- 6.40. Lofwall (2018) was the most recent variable-dose study of BUP/NAL SL tablets available and reported a daily dose of at least 19.6mg in weeks 12-24 of the study. In

addition, in weeks 12-24, supplemental weekly 8 mg SC injections of buprenorphine were administered to 17 of 215 participants (7.9%) in the BUP/NAL SL tablet group, which are not accounted in the above calculation of steady state doses. The submission assumed that the Phase 2 dosage of BUP/NAL SL tablets was steady state dosing. This was slightly higher than the 18.5mg of Phase 1, which did not include 8mg SC injections. It was likely that the frequency of visits, and number of take-home sublingual doses given contributed to differences in mean dosing. Using the dose of 19.6mg unreasonably increased the cost minimisation price.

- 6.41. The Lofwall (2018) estimate of the mean dose of BUP/NAL SL tablets was derived from trial completers. This could potentially be an overestimate. Additionally, the submission calculated equi-effective doses for BUP/NAL SL tablets, whereas the comparator is SL film. Due to differences in the bioavailability in the film and tablet, it is possible that estimates based on tablet dosing may slightly overestimate sublingual film doses.
- 6.42. The ESC considered that the equi-effective dose was overestimated, and that a more reasonable estimate of equi-effective dose is 14mg of BUP/NAL SL film daily.
- 6.43. The submission included cost offsets for GP visits, patient fees, and a price premium for being a long acting dosage form. The ESC advised that these cost-offsets are over-estimated due to potential increase in allied health services, such as psychosocial services, as a result of treatment success and GP referrals, and the nominated MBS item code 3 is unlikely to be used over MBS Item code 23.
- 6.44. The submission's claim that GP visits would be reduced was based on Larance (2009) but was also influenced by unsubstantiated assumptions. It may be more likely that GP visits would increase as Sublocade is administered monthly whereas treatment with BUP/NAL SL film would require GP visits every 3-6 months for a new script. Nevertheless, GP visits were not a key driver of the cost-minimisation price.
- 6.45. Though patient fees would be expected to be reduced, it is possible that they would not be to the degree that is estimated by the submission as some patients already access a month's supply of BUP/NAL SL film. Nevertheless, patient fees are not typically included in cost-minimisation analyses.
- 6.46. The results of the cost-minimisation analysis are presented in Table 11.

Table 11: Results of the cost-minimisation analysis

Component	Sublocade	BUP/NAL SL film	Increment
Daily cost	-	\$12.43	-
Monthly drug cost	\$ [REDACTED]	\$378.34	\$ [REDACTED]
GP visits	\$20.27	\$25.76	-\$5.49
Patient co-payments	\$50	\$199.95	-\$149.99
Adverse event	\$0.00	\$0.00	\$0.00
Cost including offsets	\$ [REDACTED]	\$604.05	\$ [REDACTED]
Long-acting premium	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Cost with offsets and premium	\$ [REDACTED]	\$604.05	\$ [REDACTED]

Source: Table 3.8, p161 of the submission

- 6.47. The submission’s claim of a long-acting injectable price premium of [REDACTED]% was based on PBAC recommendations for different medicines in a different indication, and no valid justification was presented for why such a premium would apply in opioid dependence disorder. The submission further attempted to support this premium with the claim of superiority in terms of reduced harms, and a cost-effectiveness analysis. The PSCR states that the price premium proposed is based on the application of an accepted [REDACTED]% premium for long acting injections (LAIs). The ESC considered that this was incorrect as there is no such accepted premium for all LAIs, and that price premiums for long acting injectable antipsychotics referenced by the submission were inappropriate to use as a precedent. Therefore, the ESC considered that the application of a price premium of this magnitude in the absence of reliable evidence to support a claim of superiority was inappropriate.
- 6.48. The ESC noted that BUP/NAL SL film attracted a premium over buprenorphine alone based on a claim of harm reduction due to reduced diversion; however, in practice reduction in diversion was less than claimed.
- 6.49. An additional cost-minimisation analysis was conducted during the evaluation in which the equi-effective dosing was changed to 18.5 mg/day, the patient fees and GP visit offsets were removed and alternate premiums were presented. This analysis is presented in Table 12.

Table 12: Results of the cost-minimisation analysis (evaluation)

Component	Sublocade	BUP/NAL SL film	Increment
Daily cost	-	\$11.52	-
Monthly drug cost	-	\$350.72	-
Patient fees	\$0.00	\$0.00	\$0.00
GP visits	\$0.00	\$0.00	\$0.00
Adverse event	\$0.00	\$0.00	\$0.00
Cost excluding offsets	\$350.72	\$350.72	\$0.00
Cost including long-acting premium			
Cost with 10% premium	\$385.79	\$350.72	\$35.07
Cost with 15% premium	\$403.32	\$350.72	\$52.61
Cost with 20% premium	\$420.86	\$350.72	\$70.14

Source: changes made during evaluation to 'Buprenorphine long-acting injectable (Sublocade) Section 3 Workbook.xlsx'

- 6.50. While the ESC considered that this was a more realistic estimation of equi-effective doses, it was likely to still be overestimated, and further considered that a 5% to 10% price premium may be more reasonable for the benefits likely to be realised from the use of this product. Based on an equi-effective dose of 14mg/day and a 5% to 10%

price premium range, the cost-minimised monthly drug cost of Sublocade would range from \$249.61 to \$261.49.

- 6.51. The supplementary cost-effectiveness analysis presented in the submission was not a full economic evaluation. The ESC noted that the structure and rationale of the model was very simplistic and was uninformative for decision-making due to the implications of any likely diversion not being quantified or applied in the model (both in terms of health and resource impacts). Therefore, based on the cost-effectiveness analysis, the ESC considered that it was not possible to judge whether the price premium was justified. The ESC considered that while both diversion averted and improved adherence could be modelled in a more comprehensive way, the overall benefit of conducting a formalised cost-utility analysis were unclear given the available empirical information presented in the submission. As such, the ESC considered that a cost-minimisation analysis compared to BUP/NAL SL film was more appropriate.

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

- 6.52. The drug cost per patient per year of Sublocade is \$ [REDACTED], based on 12 injections per year (one per month) of either 100mg or 300mg Sublocade at the requested price of \$ [REDACTED]. Treatment duration is indefinite with potential to be lifelong for many patients.
- 6.53. The drug cost per patient per year of the main comparator BUP/NAL SL film would be \$ [REDACTED], based on a mean daily dose of 19.6mg and an average monthly cost of \$ [REDACTED] as estimated by the submission. It was likely however, that the dosage could be lower in practice, and thus these costs were overestimated.

Estimated PBS usage & financial implications

- 6.54. This submission was not considered by DUSC. The submission used an epidemiological approach and a modified market share approach to estimate the number of patients with opioid use disorder eligible for treatment with Sublocade. Both approaches calculate the number of patients who are eligible to receive Sublocade (rather than calculating prescriptions or units dispensed).
- 6.55. The submission considered that there were two patient populations who may access Sublocade: patients currently accessing opioid dependence treatment and persons not currently accessing opioid dependence treatment. The former population was estimated with assumed replacement rates of patients currently taking BUP/NAL SL film, and the latter was estimated with a small, assumed uptake rate of patients not currently on treatment.
- 6.56. The key input for the financial estimates was uptake. It was unclear whether uptake was underestimated or overestimated given that Sublocade would constitute a new approach to treatment. The submission noted that the sponsor was willing to discuss a Risk Sharing Arrangement. This could potentially address concerns regarding uptake, however a Risk Sharing Arrangement may be challenging to implement in the context of the Opioid Dependence Treatment Program.

6.57. To the extent that uptake was accurately estimated, the submission’s estimates likely underestimated costs to government due to overestimated annual average dose of BUP/NAL SL film and slightly underestimating average annual dose of Sublocade.

6.58. Table 13 presents the submission’s estimates of use and financial implications.

Table 13: 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	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of buprenorphine long acting injection						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	\$0	\$0	\$0	\$0	\$0	\$0
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for BUP/NAL						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	\$0	\$0	\$0	\$0	\$0	\$0
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

^a Assuming █ 100mg doses and █ 300mg doses in induction (█% of patients) and █ 100mg doses per year for maintenance patients (█% of patients) as estimated by the submission. Source: Table 4.11, p174, Table 4.16, p176, Table 4.26, p180, Table 4.35, p184 and Section 4 workbook of the submission ‘cost to PBS & RPBS’ worksheet.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS/RPBS would be \$30 to \$60 million.

6.59. It was also possible that if Sublocade had improvements in compliance/adherence that was claimed in the submission patients would stay on treatment for a longer period than BUP/NAL SL film and thus more patients would be on treatment than estimated by NOPSAD data. The submission made no adjustment for this.

6.60. Utilisation of Sublocade, and the likely substitution from other opioid substitution therapies, cannot be reliably determined until the practice model is known. The uncertainties include whether the product will be supplied through a patient’s usual dispensing site (including community pharmacy) or 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 estimated reliably. Though the submission presented some information regarding proposed practice models (discussed in Section 2 above), this will remain highly dependent on agreement with State and Territory Governments and specific details regarding supplying and dispensing Sublocade.

6.61. The submission did not consider the impacts on any adjuvant psychosocial treatments (for example that increased compliance may lead to greater use of psychological

therapy) and overall the ESC considered that the MBS savings were poorly justified and unlikely to be realised. Furthermore, as cost savings from GP visits were factored into the cost-minimisation analysis, the ESC considered it inappropriate that they were also included as a financial cost offset (which are generally not included in the financial estimates in any case).

Quality Use of Medicines

- 6.62. The submission considered the availability of Sublocade to have the following quality use of medicine benefits:
- Sustained clinically meaningful benefits concerning reducing illicit opioid use with direct health and societal benefits.
 - As the treatment is administered by a professional and is not handled by the patient at any stage, there are great harm reduction benefits of zero misuse, abuse and diversion, with its resultant health and societal benefits.
 - Improved patient treatment compliance. Reasons for the non-adherence to treatment include poor disease awareness, side effects, low efficacy and complicated posology.
 - Decreased unintended paediatric exposure.
 - No known risk of accidental overdose.
 - Reduced administration and costs of treatment compared with current ODT treatments that require daily administration and supervision, including patient daily dispensing payments.
- 6.63. The sponsor was working with wholesalers to add additional warnings upon delivery of the product to health care providers.
- 6.64. The submission noted that in the absence of any agreements from jurisdictions and or health care professionals, the sponsor would delay supply of the product until such agreements can be reached.
- 6.65. Given the long acting formulation of prolonged release buprenorphine, it may be difficult to reverse the opioid effects in emergency situations, including accidental overdose. 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.
- 6.66. 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. This issue should be addressed by the sponsor in a QUM plan.

- 6.67. The safety of stopping treatment with, or weaning from, prolonged release buprenorphine was unclear and should be addressed.
- 6.68. It was 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.

Financial Management – Risk Sharing Arrangements

- 6.69. The submission noted that, if appropriate, the sponsor is willing to enter a Risk Share Arrangement to mitigate the risk to government due to an unforeseen increase in patients accessing Sublocade. The sponsor did not provide any further details.

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

7 PBAC Outcome

- 7.1. The PBAC deferred its decision on whether to recommend the Section 100 (Opiate Dependence Treatment Program) listing for buprenorphine long-acting subcutaneous injection (Sublocade®) for the treatment of opioid use disorder (OUD). However, the PBAC was of a mind to recommend Sublocade on a cost minimisation basis to sublingual buprenorphine/naloxone (BUP/NAL SL film), pending provision of a positive TGA Delegate's overview. The PBAC acknowledged there was a clinical need for an alternative form of medication assisted treatment for opioid dependence, and that a long-acting subcutaneous injection was likely to have both clinical and social advantages for some patients in this treatment setting.
- 7.2. The PBAC considered that any future listing of long-acting buprenorphine should be under the existing Section 100 (Opioid Dependence Treatment Program) noting the supply of the drug would be restricted to approved prescribers who would also administer the dose, and that this was most likely to occur in a general practice setting. The PBAC considered that this is a significant shift away from the current community pharmacy based model. The PBAC further noted that implementation of any future positive recommendation would require significant liaison with states and territories.
- 7.3. The PBAC considered the nominated comparator, BUP/NAL SL film, was appropriate, and that buprenorphine prolonged release subcutaneous injection (Buvidal®), was also an appropriate near market comparator.
- 7.4. The PBAC acknowledged the limitations in the indirect comparisons presented between Sublocade and BUP/NAL SL film, and between Sublocade and Buvidal, and agreed with the ESC that, on balance, it was reasonable to accept that Sublocade was non-inferior in comparative efficacy and safety to the comparators.
- 7.5. The PBAC did not accept that Sublocade was superior to BUP/NAL SL film in terms of harm reduction.

- 7.6. The PBAC recognised that there were potential benefits of having a long-acting injectable treatment available for patients seeking treatment for opioid use disorder, including retention in treatment and reduced risk of diversion.
- 7.7. The PBAC considered that a listing of Sublocade would be acceptably cost-effective if it was cost minimised to BUP/NAL SL film based on drugs costs alone, excluding patient fees and GP costs, with a modest price premium to recognise the potential benefits of having a long-acting injectable treatment available. If Sublocade and Buvidal were both PBS-listed, the PBAC advised that the price of Sublocade should be no higher than the price of Buvidal on a drug cost per patient per day basis. The PBAC did not accept the submission's request for a long-acting injectable price premium of ■%, and instead considered that a modest price premium of 10-15% over BUP/NAL SL film would be reasonable in this context.
- 7.8. The PBAC considered the estimates of utilisation were reasonable, however noted there was some uncertainty as to the expected uptake of the prolonged release injection form of buprenorphine, particularly noting that the practice model is not yet known. The PBAC noted that as the drug cost per patient for Sublocade will be lower than estimated in the submission when the above parameters are adopted, the financial estimates would appropriately be reduced from those estimated in the submission.
- 7.9. The PBAC noted that quality use of medicines issues including difficulty in reversing prolonged release buprenorphine in emergency situations, difficulty in managing pain, difficulty in managing the risk of CNS depression in cases of poly drug use, safety in stopping (weaning off) treatment, and treatment effects of reducing regular visits to a healthcare providers were all relevant considerations for prescribers when choosing to prescribe Sublocade to patients.

Outcome:

Deferred

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

The sponsor had no comment.