

**7.16 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<sup>®</sup>, Camurus AB.**

**1 Purpose of Application**

- 1.1 The minor resubmission sought a Section 100 (Opiate Dependence Treatment Program) listing for prolonged release subcutaneous injection of buprenorphine for the treatment of opioid dependence.
- 1.2 The resubmission included a [REDACTED] % price reduction based on a cost-minimisation analysis as outlined by the PBAC in the November 2018 major submission.

**2 Requested listing**

- 2.1 In November 2018, the PBAC considered the proposed Section 100 listing was appropriate and consistent with existing Section 100 (Opiate Dependence) listings.

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 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 Camurus AB
96 mg in 0.27 mL	1	NA	\$ [REDACTED]	
128 mg in 0.36 mL	1	NA	\$ [REDACTED]	

<b>Category / Program</b>	Section 100 Opiate Dependence
---------------------------	-------------------------------

<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Opiate dependence
<b>PBS Indication:</b>	Opiate dependence
<b>Restriction Level / Method:</b>	<input checked="" 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
<b>Treatment criteria:-</b>	The treatment must be administered by a health care professional.
<b>Clinical criteria:</b>	The treatment must be within a framework of medical, social and psychological treatment.
<b>Administrative Advice</b>	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

- 2.2 At its November 2018 meeting, the PBAC advised that the proposed listing would require significant liaison with states and territories noting the supply of the drug would be restricted to approved prescribers who would also administer the dose and this was a significant shift away from the current community pharmacy based model. (Public Summary Document (PSD) November 2018 PBAC Meeting, paragraph 7.11).
- 2.3 The proposed PBS restriction was silent on age, but was otherwise consistent with the approved TGA indication.
- 2.4 Both Buvidal Weekly and Buvidal Monthly are to be initiated following stabilisation on sublingual buprenorphine or buprenorphine/naloxone for at least 7 days. This could be added into the PBS restriction to ensure patients do not initiate treatment with prolonged release buprenorphine.
- 2.5 The existing PBS listing for sublingual buprenorphine/naloxone in opiate dependence allows 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.

### 3 Background

- 3.1 Prolonged release buprenorphine was TGA registered on 28 November 2018 for maintenance treatment of opioid dependence within a framework of medical, social, and psychological treatment.
- 3.2 At its November 2018 meeting, the PBAC considered prolonged release buprenorphine. The PBAC did not recommend the listing of prolonged release buprenorphine on the basis that the evidence provided did not adequately support

the claim of superior comparative effectiveness, and therefore the request for a higher price for this treatment compared to existing treatments for opiate dependence was not justified.

- 3.3 At its November 2018 meeting, 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 (Public Summary Document (PSD) November 2018 PBAC Meeting, paragraph 7.12).
- 3.4 For more detail on PBAC's view, see section 7 PBAC outcome.

## **4 Population and disease**

- 4.1 The target population in the submission was people with opioid dependence/opioid use disorder. 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.
- 4.2 At the November 2018 meeting, the PBAC acknowledged 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 (Public Summary Document (PSD) November 2018 PBAC Meeting, paragraph 7.2)
- 4.3 A major submission for another brand of long acting buprenorphine injection (Sublocade, sponsored by Indivior Pty Ltd) was considered by the PBAC at its March 2019 meeting for the same indication.
- 4.4 For more detail on PBAC's view, see section 7 PBAC outcome

## **5 Comparator**

- 5.1 The PBAC previously accepted that sublingual buprenorphine/naloxone was the appropriate main comparator. This was unchanged in the minor submission.
- 5.2 For more detail on PBAC's view, see section 7 PBAC outcome

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

- 6.2 There were no consumer comments for this item.

### **Clinical trials**

6.3 As a minor submission, no new clinical trials were presented in the resubmission.

### **Clinical claim**

6.1 Unchanged from the November 2018 major submission, the minor resubmission claimed superior comparative effectiveness and non-inferior comparative safety of prolonged release buprenorphine compared with sublingual buprenorphine/naloxone. The PBAC had previously considered the claim of superiority was not supported, however, the minor submission maintained superiority was demonstrated by the cumulative distribution function (CDF) in reducing the illicit opioid use in patients who did not achieve near to full abstinence.

6.2 The minor resubmission provided additional context around interpreting CDF as an outcome measure, noting that the focus of opioid dependency management was moving away from a treatment goal of continuous abstinence towards a goal of harm reduction. It was highlighted that the CDF considers a range of individual responder definitions from abstinence to complete non-responders, rather than a binary (abstinent or not-abstinent) result.

6.3 The minor resubmission maintained that there were additional benefits to treatment that supported the clinical claim, including improved treatment retention, negation of diversion, and increased capacity for treatment.

6.4 At its November 2018 meeting, 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.

6.5 The PBAC previously accepted the claim of non-inferior comparative safety to sublingual buprenorphine/naloxone.

### **Economic analysis**

6.6 Table 1 outlines the PBAC's previous key concerns with the economic evaluation and how these were addressed in the minor resubmission.

**Table 1: Summary of outstanding matters of concern with the economic evaluation from November 2018**

<i>Previous PBAC concern</i>	<i>How addressed in minor resubmission</i>
The PBAC considered a cost-minimisation analysis compared to sublingual buprenorphine/naloxone would be appropriate.(Para 7.8)	The minor resubmission presented a cost-minimisation analysis compared to sublingual buprenorphine/naloxone based on GP implementation model. The revised price offer proposed in the submission was \$ [redacted] per day, a [redacted] % price reduction from that proposed in the major submission (\$ [redacted]).
The PBAC considered that a modest price premium may be acceptable in acknowledgement of the unquantifiable benefits of a new treatment option. (Para 7.8)	The minor resubmission proposed a [redacted] % price premium over sublingual buprenorphine/naloxone based on the additional benefits of reduced diversion, misuse, improved retention, reduction in service fees and reduced stigma.

Source: Compiled during preparation of the minor overview

- 6.7 The minor resubmission presented a cost-minimisation analysis (including a [redacted] % price premium) of prolonged release buprenorphine compared with sublingual buprenorphine/naloxone based on an equivalent cost per day with a GP-based section 100 implementation model. The submission’s cost-minimisation analysis was performed based on 28 days of treatment with sublingual buprenorphine/naloxone.
- 6.8 The resubmission stated that the steady state mean dose of sublingual buprenorphine/naloxone from HS-11-421 trial (18.34 mg/day) and relative utilisation of the 8 mg/2 mg and 2 mg/0.5 mg dose formulations from 2017 IMS data were used to estimate the equi-effective doses. Based on this estimate, the equi-effective doses are:
- Buvidal 50mg/mL weekly and Buvidal 356mg/mL monthly are equivalent to 18.34mg sublingual buprenorphine/naloxone daily.
- 6.9 The resubmission proposed a price of sublingual buprenorphine/naloxone based on this equi-effective dose of \$ [redacted] per day. This was different to the cost of \$ [redacted] per day proposed in the November 2018 major submission. The minor resubmission stated that the original cost-minimised price was conservatively based the costs per day on the lower priced sublingual buprenorphine/naloxone (BPN 8 mg + NX 2 mg) and it considered it reasonable that the cost minimisation analysis included the costs of both formulations of sublingual buprenorphine/naloxone.
- 6.10 The table below outlines the calculation of sublingual buprenorphine drug costs in the cost-minimisation analysis.

**Table 2: Calculation of drug costs in the cost-minimisation analysis**

Row	Formulation	BPN 2 mg + NX 500 µg	BPN 8 mg + NX 2 mg	Totals	Reference / Calculations
A	BPN strength (mg)	2	8	-	PBS items 9749D 9750E
B	Quantity	28	28	-	
C	Price	\$46.20	\$132.44	-	
D	Price/mg (of BPN)	\$0.825	\$0.59125	-	C / (AxB)
E	Units dispensed	██████	██████	██████	2017 IMS data
F	BPN mg dispensed used	██████	██████	██████	A x B x E
G	Proportion MG used	██%	██%	██%	F/Sum(F)
H	Weighted average price per mg			\$██████	Sum of average of Row D by weights in Row G
I	BPN dose per day (mg)			18.34	Steady state mean dose of SL BPN/NX from HS-11-421 trial
J	BPN/NX cost per day			\$██████	H x I

Source: Table 6, p.24 of the March 2019 minor resubmission  
Abbreviations: BPN buprenorphine; NX naloxone.

6.11 The minor resubmission proposed a cost per day of \$██████ for prolonged release buprenorphine that included a price premium of ███% based on additional benefits of reduced diversion, misuse, improved retention, reduction in service fees and reduced stigma. A service model cost savings of \$██████ was also included in the analysis based on the difference between the GP clinic model and the community pharmacy model. The submission claimed this represented a ███% price reduction from \$██████ proposed in the major submission. The table below outlines the calculation of prolonged release buprenorphine drug costs used in the cost-minimisation analysis.

**Table 3: Calculation of prolonged release buprenorphine in the cost-minimisation analysis**

Row	Price of CAM2038, by component	Value	Source / method
A	Drug cost cost-minimisation (i.e. BPN/NX cost per day)	\$██████	Row J, Table 2 above.
B	Price premium	\$██████	██% of BPN/NX equivalent cost per day
C	Service model cost savings (per day)	\$██████	Cost savings from a community pharmacy model of CAM2038
D	Proposed price of CAM2038 per day	\$██████	A + B + C
E	Reduction from last submission (\$██████)	██%	

Source: Table 8, p.24 of the March 2019 minor resubmission  
Abbreviations: CAM2038, prolonged release buprenorphine.

6.12 The service model cost savings estimated in the resubmission may not be reasonable. The submission proposed that Section 85 PBS mark-up fees including mark-ups, dispensing and dangerous drug fees, and a delivery fee, are utilised as a proxy for private fees charged to patients. The resubmission stated this was in response to PBAC concerns that dispensing sites could elect to charge private fees (Public Summary

Document (PSD) November 2018 PBAC Meeting, paragraph 2.7). The weighted cost for private fees was \$48.46 for prolonged release buprenorphine, and \$129.64 for sublingual buprenorphine/naloxone. It may be more appropriate to remove all private fees for both prolonged release buprenorphine and sublingual buprenorphine/naloxone, and instead include only PBS and MBS costs in the cost-minimisation analysis. The results of this are presented in the table below. This instead results in an additional \$ [REDACTED] service model cost instead of a \$ [REDACTED] service model saving.

**Table 4: Results of the revised cost-minimisation analysis**

Component	CAM2038	SL BUP/NX	Increment
Drug cost cost-minimisation	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
GP Prescribing	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Drug administration/Supervision	\$ [REDACTED]	\$0	\$ [REDACTED]
Pharmacy Dispensing	\$0	\$0	\$0
<b>Daily Costs</b>			
Drug cost per day	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Service model costs (per day)	\$ [REDACTED]		
Price reduction from November 2018 submission % (\$ [REDACTED])	- [REDACTED]%		

Source: Compiled during the evaluation of the March 2019 minor submission

Abbreviations: CAM2038, prolonged release buprenorphine; SL BPN/NX, sublingual buprenorphine/naloxone

6.13 Additional uncertainties in the cost minimisation analysis included the equi-effective dose of sublingual buprenorphine/naloxone and the GP prescribing costs, which may have been overestimated in the sublingual buprenorphine/naloxone arm as these patients may receive a prescription for more than 1 months' supply.

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

6.14 At the proposed price, the drug cost per patient per year of prolonged release buprenorphine was \$ [REDACTED], based on an equi-effective dose of sublingual buprenorphine/naloxone of 18.34mg and a cost per day of \$ [REDACTED]. Treatment duration is indefinite with potential to be lifelong for many patients.

**Estimated PBS usage & financial implications**

6.15 The minor resubmission provided updated utilisation data from the National Opioid Pharmacotherapy Statistics (NOPSAD-2017) and PBS reported expenditure to forecast the cost of each drug within the program over the next 6 years. The model provided with the submission has been updated to account for market growth within the current market share analysis.

6.16 At its November 2018 meeting, the PBAC considered the likely substitution from other opioid substitution therapies cannot be reliably determined until the practice model is

known (Public Summary Document (PSD) November 2018 PBAC Meeting, paragraph 7.9). However, unchanged from the major submission the minor resubmission assumed uptake rates of prolonged release buprenorphine are not expected to exceed █% and the rates of substitution from existing Medication Assisted Treatment (MAT) are expected to be 90% from sublingual buprenorphine (SL BPN) and 10% from methadone.

- 6.17 The market share approach used in the previous major submission did not capture patients who, previously not treated, may initiate opioid substitution therapy due to the convenience of monthly injections and a practice model delivered through general practice. In the revised utilisation estimates, the resubmission assumed 25% of prolonged release buprenorphine would be utilised in patients not otherwise treated. The submission based this calculation on a hazard ratio for improved retention to treatment of 1.25.
- 6.18 The PBAC noted the Pre-PBAC response requested a special pricing arrangement (SPA) maintaining prolonged release buprenorphine has unique characteristics compared to alternative therapies and treats a significant medical condition. The Pre-PBAC response requested a published price of \$█ with a SPA rebate of █% to reach the proposed effective price of \$█. The PBAC agreed with the pre-PBAC response that prolonged release buprenorphine has unique characteristics due to the method of administration.
- 6.19 The resubmission estimated the overall net budget impact to the PBS was less than \$10 million in the first year of listing, increasing to \$20 to \$30 million by the sixth year of listing. This was compared to \$20 to \$30 million over 6 years in the November 2018 major submission. The resubmission stated the sponsor was willing to discuss a Risk Sharing Arrangement if necessary. The table below summarise the expected patient numbers and total costs.

**Table 5: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■	■	■	■	■	■
<b>Estimated financial implications of prolonged release buprenorphine</b>						
Cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Co-payments	N/A	N/A	N/A	N/A	N/A	N/A
Cost offsets for substituted therapies	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■

Source: Table 9, pp 28-29 of the submission

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.*

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Section 100 (Opiate Dependence Treatment Program) listing for buprenorphine prolonged release subcutaneous injection (Buvidal®) for the treatment of opioid dependence based on a cost minimisation basis with sublingual buprenorphine/naloxone. The PBAC acknowledged there was a clinical need for an alternative form of medication assisted treatment for opioid dependence, and that a prolonged release injection was likely to have both clinical and social advantages for some patients in this treatment setting.
- 7.2 The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of Buvidal would be acceptable on the basis that it is cost minimised to sublingual buprenorphine/naloxone based on drugs costs alone, with a price premium to recognise the potential benefits of having a long-acting injectable treatment available that included retention in treatment and reduced risk of diversion. The PBAC advised that Buvidal 50 mg/mL weekly or Buvidal 356 mg/mL monthly is equi-effective to 18.34 mg sublingual buprenorphine/naloxone daily.
- 7.3 The PBAC accepted the proposed restriction wording, noting it was consistent with the restriction for sublingual buprenorphine/naloxone, with the exception that a health care professional must administer treatment. The PBAC noted the finalised TGA product information that recommended that both Buvidal Weekly and Buvidal

Monthly are to be initiated following stabilisation on sublingual buprenorphine or buprenorphine/naloxone for at least 7 days. The PBAC therefore considered that it would be appropriate to include the statement ‘the patient must be stabilised on sublingual buprenorphine/naloxone or buprenorphine prior to commencing treatment with this drug for this condition’ in the restriction.

- 7.4 The PBAC reaffirmed its November 2018 advice that, based on the evidence provided in the submission, prolonged release buprenorphine injection was non-inferior in terms of comparative efficacy and safety to sublingual buprenorphine/naloxone.
- 7.5 The PBAC considered that the cost-minimisation analysis presented in the resubmission included drug costs, GP prescribing and administration costs, pharmacy dispensing, and private patient fees, and considered that this resulted in a cost-minimised price of uncertain cost-effectiveness. In particular, PBAC considered that MBS costs could not be reliably estimated until the practice model is known following implementation, and that it was inappropriate to include private patient fees in the cost-minimisation analysis. Further, the PBAC noted the potential for higher daily costs of prolonged release buprenorphine injection if multiple products of varying strength were used in a single administration. On that basis, the PBAC considered the most appropriate approach to the cost-minimisation was based on drug costs alone, flat priced on a per day basis across strengths, at an equi-effective dose of 18.34mg/day of sublingual buprenorphine/naloxone, with a ■■■% price premium. This results in a cost per day lower than estimated in the resubmission.
- 7.6 The PBAC considered the utilisation and financial estimates were reasonable, however noted there was some uncertainty as to the expected uptake of the prolonged release injection form of buprenorphine.
- 7.7 The PBAC recalled at its November 2018 meeting that implementation of a positive recommendation would require significant liaison with the states and territories, and that previously raised issues concerning the Quality Use of Medicines (QUM) would require resolution prior to implementation. These QUM issues included 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 (Public Summary Document (PSD) November 2018 PBAC Meeting, paragraphs 6.70 - 6.77).
- 7.8 The PBAC noted that the pre-PBAC response requested a Special Pricing Arrangement (SPA), and while it agreed that the medicine has unique characteristics compared to available treatments for opioid dependence, it did not consider that prolonged release buprenorphine provided a substantial incremental benefit over existing treatments.
- 7.9 The PBAC advised that buprenorphine is not interchangeable with any other drugs or medicinal preparations on an individual patient basis.

- 7.10 The PBAC advised that prolonged release buprenorphine is suitable for prescribing by nurse practitioners within a shared care model.
- 7.11 The PBAC recommended that the Early Supply Rule should apply.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

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

<b>Category / Program</b>	Section 100 Opiate Dependence
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Opiate dependence
<b>PBS Indication:</b>	Opiate dependence
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Restricted benefit
<b>Treatment criteria:-</b>	The treatment must be administered by a health care professional.
<b>Clinical criteria:</b>	The treatment must be within a framework of medical, social and psychological treatment. AND The patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition
<b>Administrative Advice</b>	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

## 9 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.

## **10 Sponsor's Comment**

Camurus are pleased the PBAC has given a positive recommendation for Buvidal and recognised that Buvidal is likely to have both clinical and social advantages for patients seeking treatment for opioid dependence. Camurus looks forward to working closely with the TGA, PBS and individual State Health Departments to implement an appropriate practice model, to ensure that healthcare professionals and patients get access to this innovative advance in treatment.

Camurus would also like to note the use of multiple products of varying strengths in a single administration referred to by PBAC is against the approved product information and would absolutely discourage this practice.