

5.05 BUPRENORPHINE

**Injection (modified release) 8 mg in 0.16 mL
pre-filled syringe,
Injection (modified release) 16 mg in 0.32 mL
pre-filled syringe,
Injection (modified release) 24 mg in 0.48 mL
pre-filled syringe,
Injection (modified release) 32 mg in 0.64 mL
pre-filled syringe,
Buvidal® Weekly,
Injection (modified release) 64 mg in 0.18 mL
pre-filled syringe,
Injection (modified release) 96 mg in 0.27 mL
pre-filled syringe,
Injection (modified release) 128 mg in 0.36 mL
pre-filled syringe,
Injection (modified release) 160 mg in 0.45 mL
pre-filled syringe,
Buvidal® Monthly,
Camurus Pty Ltd**

1 Purpose of submission

- 1.1 Prolonged release buprenorphine has a Section 100 Opiate Dependence Treatment Program (ODTP) listing on the PBS for opiate dependence in patients who are stabilised on sublingual buprenorphine or buprenorphine/naloxone.
- 1.2 The purpose of the submission was to:
 - Request a Section 85 (Restricted Benefit) listing in addition to the current Section 100 (ODTP).
 - Request a change to the PBS restriction to remove the requirement that a patient must be stabilised on sublingual buprenorphine or sublingual buprenorphine/naloxone prior to commencing treatment with prolonged release buprenorphine,

consistent with the recent amendment to the TGA indication (for weekly prolonged release buprenorphine).

- Request the inclusion of an additional dose of monthly prolonged release buprenorphine (160 mg in 0.45 mL), consistent with recent TGA approval of this dose.
- Request a price increase consistent with the requested price in the March 2019 minor resubmission, based on a cost-minimisation analysis versus sublingual buprenorphine/naloxone, incorporating practice model cost savings associated with the PBS listing of prolonged release buprenorphine.
- Update the financial implications to account for a dual Section 85/Section 100 listing and an increased price for prolonged release buprenorphine.

2 Background

Registration status

- 2.1 Prolonged release buprenorphine was first registered by the TGA on 28 November 2018 for maintenance treatment of opioid use disorder within a framework of medical, social, and psychological treatment. The product information at that time noted that both weekly and monthly prolonged release buprenorphine are to be initiated following stabilisation on sublingual buprenorphine or buprenorphine/naloxone for at least 7 days.
- 2.2 The following revised indications for weekly and monthly prolonged release buprenorphine were approved on 29 April 2021:
 - Weekly prolonged release buprenorphine is indicated for initiation and maintenance treatment of opioid dependence, with or without prior stabilisation on sublingual buprenorphine or buprenorphine/naloxone, within a framework of medical, social and psychological support.
 - Monthly prolonged release buprenorphine is indicated for maintenance treatment of opioid use disorder with prior stabilisation on weekly prolonged release buprenorphine or sublingual buprenorphine or buprenorphine/naloxone within a framework of medical, social and psychological support.
- 2.3 Amendments to the prolonged release buprenorphine indication and product information include the addition of a 160 mg monthly dosage, revised separate indications for weekly and monthly prolonged release buprenorphine, and removal of the requirement for stabilisation on sublingual buprenorphine prior to commencing weekly prolonged release buprenorphine.

Previous PBAC consideration

- 2.4 Prolonged release buprenorphine was listed on the PBS under the Section 100 Opiate Dependence Treatment Program (ODTP) for the treatment of opioid use disorder in September 2019 following a submission in November 2018 and a minor resubmission in March 2019.

3 Requested listing

3.1 The following changes to the PBS listing were proposed in the submission:

- A Section 85 (Restricted Benefit) listing in addition to the current Section 100 (ODTP) listing.
- Removal of the requirement for stabilisation on sublingual buprenorphine prior to initiation with prolonged release buprenorphine.
- The addition of a 160 mg in 0.45 mL dose of the monthly prolonged release formulation.
- A higher ex-manufacturer price for both the weekly and monthly prolonged release formulations compared to the current PBS prices (\$92.40 and \$369.60, respectively), based on a cost minimisation analysis incorporating practice model cost savings associated with the PBS listing of prolonged release buprenorphine.

Name, Restriction, Manner of administration and form	Max. Qty (units)	№.of Rpts	Price ex-manufacturer (\$)	Proprietary Name and Manufacturer
BUPRENORPHINE 50 mg/mL weekly subcutaneous depot injection, pre-filled syringe				BUVIDAL Camurus Pty Ltd
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, pre-filled syringe				BUVIDAL Camurus Pty Ltd
64 mg in 0.18 mL	1	NA		
96 mg in 0.27 mL	1	NA		
128 mg in 0.36 mL	1	NA		
160 mg in 0.45 mL	1	NA		
Category/Program:	GENERAL – General Schedule (Code GE) Section 100 – Opiate Dependence			
PBS indication:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners			
Condition:	Opiate dependence			
PBS Indication:	Opiate dependence			
Restriction:	Restricted benefit			
Treatment criteria:	Must be treated by a health care professional			
Clinical criteria:	The treatment must be within a framework of medical, social and psychological treatment. Patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition.			
Administrative advice:	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.			

Note: Changes/additions to the current PBS listing are bolded, and deletions in strikethrough.

- 3.2 Based on the proposed ex-manufacturer prices, the dispensed prices under the proposed Section 85 listing for weekly and monthly prolonged release buprenorphine would be \$ [REDACTED] and \$ [REDACTED], respectively.
- 3.3 The proposed restriction is based on the current PBS restriction for buprenorphine modified release injections, excluding the requirement for prior stabilisation on sublingual buprenorphine or buprenorphine/naloxone, and is consistent with the TGA approved indication for weekly prolonged release buprenorphine. However, the proposed restriction is inconsistent with the TGA approved indication for monthly prolonged release buprenorphine, which requires prior stabilisation on weekly prolonged release buprenorphine, sublingual buprenorphine, or buprenorphine/naloxone. The evaluation considered that separate restrictions for initiation (for weekly prolonged release buprenorphine) and maintenance treatment (for weekly and monthly prolonged release buprenorphine) may be required.
- 3.4 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. Red text indicates the sponsor's proposed changes to the existing restriction.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BUPRENORPHINE 50 mg/mL weekly					
Buprenorphine 8 mg/0.16 mL modified release injection, 0.16 mL syringe	11759X	1	1	NA	Buvidal weekly
Buprenorphine 16 mg/0.32 mL modified release injection, 0.32 mL syringe	11774Q				
Buprenorphine 24 mg/0.48 mL modified release injection, 0.48 mL syringe	11773P				
Buprenorphine 32 mg/0.64 mL modified release injection, 0.64 mL syringe	11766G				
Restriction Summary 9213 / Treatment of Concept: 9212					
Section 100 – Opiate Dependence					
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					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					
Administrative Advice: Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.					
Administrative Advice: 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.					
Indication: Opiate dependence					
Treatment criteria:					
Must be treated by a health care professional					
AND					

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Clinical criteria:
The treatment must be within a framework of medical, social and psychological treatment
AND
Clinical criteria:
Patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BUPRENORPHINE 356 mg/mL monthly					
Buprenorphine 64 mg/0.18 mL modified release injection, 0.18 mL syringe	11754P	1	1	NA	Buvidal Monthly
Buprenorphine 96 mg/0.27 mL modified release injection, 0.27 mL syringe	11767H				
Buprenorphine 128 mg/0.36 mL modified release injection, 0.36 mL syringe	11768J				
<i>Buprenorphine 160 mg/0.45 mL modified release injection, 0.45 mL syringe</i>	<i>NEW</i>				

Restriction Summary 9213 / Treatment of Concept: 9212

Section 100 – Opiate Dependence	
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	
Restriction type: <input checked="" type="checkbox"/> Restricted benefit	
Administrative Advice:	Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.
Administrative Advice:	
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.
Indication: Opiate dependence	
Treatment criteria:	
Must be treated by a health care professional	
AND	
Clinical criteria:	
The treatment must be within a framework of medical, social and psychological treatment	
AND	
Clinical criteria:	
Patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition	
<i>Patient must be stabilised on one of the following prior to commencing treatment with this drug for this condition: (i) weekly prolonged release buprenorphine (Buvidal Weekly) (ii) sublingual buprenorphine (iii) buprenorphine/naloxone</i>	

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BUPRENORPHINE 50 mg/mL weekly					
Buprenorphine 8 mg/0.16 mL modified release injection, 0.16 mL syringe	NEW	1	1	NA	Buvidal weekly
Buprenorphine 16 mg/0.32 mL modified release injection, 0.32 mL syringe	NEW				
Buprenorphine 24 mg/0.48 mL modified release injection, 0.48 mL syringe	NEW				
Buprenorphine 32 mg/0.64 mL modified release injection, 0.64 mL syringe	NEW				
Restriction Summary 9213 / Treatment of Concept: 9212					
Category / Program: GENERAL- General Schedule					
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					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					
Administrative Advice: Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.					
Administrative Advice: 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.					
Indication: Opiate dependence					
Treatment criteria:					
Must be treated by a health care professional					
AND					
Clinical criteria:					
The treatment must be within a framework of medical, social and psychological treatment					
AND					
Clinical criteria:					
Patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
BUPRENORPHINE 356 mg/mL monthly					
Buprenorphine 64 mg/0.18 mL modified release injection, 0.18 mL syringe	NEW	1	1	NA	Buvidal Monthly
Buprenorphine 96 mg/0.27 mL modified release injection, 0.27 mL syringe	NEW				
Buprenorphine 128 mg/0.36 mL modified release injection, 0.36 mL syringe	NEW				
<i>Buprenorphine 160 mg/0.45 mL modified release injection, 0.45 mL syringe</i>	<i>NEW</i>				
Restriction Summary / Treatment of Concept:					
Category / Program: GENERAL- General Schedule					
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					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					

	<p>Administrative Advice: Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.</p>
	<p>Administrative Advice: 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.</p>
	<p>Indication: Opiate dependence</p>
	<p>Treatment criteria: Must be treated by a health care professional</p>
	<p>AND</p>
	<p>Clinical criteria: The treatment must be within a framework of medical, social and psychological treatment</p>
	<p>AND</p>
	<p>Clinical criteria: Patient must be stabilised on sublingual buprenorphine or buprenorphine/naloxone prior to commencing treatment with this drug for this condition <i>Patient must be stabilised on one of the following prior to commencing treatment with this drug for this condition: (i) weekly prolonged release buprenorphine (Buvidal Weekly) (ii) sublingual buprenorphine (iii) buprenorphine/naloxone</i></p>

- 3.5 The Pre-Sub-Committee Response (PSCR) proposed restriction wording for the monthly formulation that includes the need to be stabilised on either the weekly formulation, sublingual buprenorphine, or sublingual buprenorphine/naloxone (whilst removing any reference to stabilisation for the weekly formulation). The ESC considered that these restriction changes regarding prior stabilisation were reasonable and supported by the clinical evidence (see paragraph 6.35).
- 3.6 The November 2018 submission for prolonged release buprenorphine requested a Section 100 listing to align with other listed opioid substitution therapy (OST). It was also proposed that the PBAC consider whether a Section 85 listing would be more appropriate on the basis that the requirement for administration by a healthcare professional in contrast with supervised dose administration at a community pharmacy for existing therapies necessitated the development of new models of care for the treatment of opioid dependence.
- 3.7 In October 2018, the ESC considered that it was more appropriate for a listing to occur under Section 100, as a General Schedule listing was unlikely to be implementable, as it would preclude some incarcerated people from accessing treatment, and a General Schedule listing whereby the medicine would be delivered directly to prescribers' rooms instead of the pharmacy would breach the conditions of approval of Section 90 (community) pharmacy (para 2.4, Buprenorphine Public Summary Document (PSD), November 2018 PBAC meeting).
- 3.8 In November 2018, the PBAC considered that any future listing of prolonged release buprenorphine should be implemented under the existing Section 100 Opioid Dependence Treatment Program (para 7.11, Buprenorphine PSD, November 2018

PBAC meeting) and the March 2019 minor resubmission requesting a Section 100 listing only was subsequently recommended.

- 3.9 The current submission proposed a dual Section 85/Section 100 (ODTP) listing whereby a General Schedule listing would be applicable to the dispensing and provision of supply of prolonged release buprenorphine by community pharmacies, and a Section 100 listing would continue to apply in other settings, including public and private specialist clinics, correctional facilities, and hospitals.
- 3.10 The submission stated that the different mechanism of administration of prolonged release buprenorphine, with administration by a healthcare professional as opposed to supervised dose administration at a community pharmacy, necessitates adaptations to the models of care for the treatment of opioid dependence and presents an opportunity to improve current PBS arrangements.
- 3.11 Recent National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) show that community pharmacy accounted for 71% of OST supply and was similarly the primary mechanism for facilitating the supply of prolonged release buprenorphine (56.9%) in Australia in 2020 (all states and territories excluding NSW as NSW buprenorphine data are not disaggregated). The submission argued that, given the majority of prolonged release buprenorphine is dispensed through pharmacies, it is currently effectively being managed as a Section 85 product, but not remunerated as such, leading to substantial out-of-pocket costs for patients.
- 3.12 The submission claimed that the advantages of a Section 85 listing for patients and service providers include:
- appropriate reimbursement of community pharmacies and wholesalers for the handling, storage and dispensing of Schedule 8 drugs consistent with the supply of other PBS listed medicines such as buprenorphine patches. The ESC acknowledged service models may incur additional costs. The ESC considered this would be informed by the current ODTP Post-market Review, which will consider service delivery arrangements.
 - standardised patient fees (copayments) which also contribute to a patient's overall PBS safety net threshold instead of private, generally unregulated pharmacy-directed service fees, which can be a barrier to access. The ESC considered that the sponsor's own survey of dispensers (n=11) indicated that, for most of them, a Section 85 listing would not stop the charging of additional, unregulated 'delivery' fees.
 - supply would not be restricted to pharmacies approved for OST services (provided appropriate contingencies are made to ensure that prolonged release buprenorphine is not dispensed directly to a patient and can be delivered to the site at which administration occurs), facilitating improved treatment access, particularly for patients in rural and remote settings. The ESC considered this may not be reasonable, noting that nearly 90% of dosing occurs in pharmacies, with many pharmacies already approved for ODTP (approximately 50%).

- 3.13 The submission noted that a dual Section 85/Section 100 Highly Specialised Drugs Program approach has been adopted for medicines used to treat hepatitis C, to ensure broad access while conforming to state and territory regulatory requirements and that similar proposals to expand the PBS listing arrangements of prolonged release buprenorphine preparations have been proposed by other stakeholders, including Harm Reduction Australia (Harm Reduction Australia MATOD Summit Report 2018; Harm Reduction Australia communiques 1-4).
- 3.14 On 24 March 2021 the Department of Health announced it would conduct a Post-market Review of the medicines available under the PBS ODTP. The Post-market Review will examine issues such as barriers to access and the future delivery of opioid use disorder treatment. The PSCR considered that the Post-Market Review will likely examine some of the issues identified in the submission, but stated that “it could be a number of years before any meaningful improvements to access are implemented”. The ESC considered that the request for a dual Section 85/Section 100 (ODTP) listing should be informed by the Post-Market Review.

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. Regular use of opioids can lead to opioid use disorder, which is a neuro-behavioural 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. In October 2018, DUSC noted that the demographics of opioid use disorder are changing, with increasing misuse of prescription opioids in place of illicit opioids (Buprenorphine DUSC Advice, November 2018 PBAC meeting).
- 4.2 Evidence-based interventions for opioid use disorder 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 use disorder with a legally obtained, long-lasting opioid which eliminates withdrawal symptoms and cravings or blocks the euphoric effect of opioid use.
- 4.3 The medications currently listed on the PBS for long-term maintenance treatment for patients with opioid use disorder are methadone, sublingual buprenorphine, sublingual buprenorphine/naloxone, and prolonged release buprenorphine. An alternative brand of prolonged release buprenorphine (Sublocade®) was listed on the PBS in May 2020 following consideration by the PBAC in March 2019 and November 2019.
- 4.4 The Royal Australasian College of Physicians produced Interim guidance for the delivery of medication assisted treatment of opioid use disorder in response to COVID-19 (RACP, April 2020), intended to be read alongside state/territory jurisdictional

advice. The key principle of the guidelines is to reduce the spread of COVID-19 amongst patients receiving opioid agonist treatment and treatment providers by reducing social exposure and attendance of patients to health services. The guidelines note the potential advantages of using prolonged release buprenorphine products in the COVID-19 context (reduced need for regular attendance for dosing, reduced need for risk assessments and reduced staff and/or patient costs associated with preparation of take-away doses of methadone and sublingual buprenorphine). The guidelines recommend maintaining patients on weekly or monthly prolonged release buprenorphine wherever possible and note that patients may initiate OST with weekly prolonged release buprenorphine before progressing to the monthly formulation.

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

5 Comparator

- 5.1 The submission did not formally nominate a comparator; however, sublingual buprenorphine/naloxone was presented as the main comparator in the majority of the clinical evidence, the cost minimisation analysis and financial implications of the submission (this is unchanged from the November 2018 and March 2019 submissions).
- 5.2 In November 2018 and March 2019, the PBAC accepted sublingual buprenorphine/naloxone as the appropriate main comparator (para 7.3, Buprenorphine Public Summary Document (PSD), November 2018 PBAC meeting; para 5.1, Buprenorphine PSD, March 2019 PBAC meeting). The PBAC considered that any OST 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 (para 7.3, Buprenorphine PSD, November 2018 PBAC meeting).
- 5.3 An alternative brand of prolonged release buprenorphine (Sublocade) was listed on the PBS in May 2020 following consideration by the PBAC in March 2019 and November 2019. Sublocade (with monthly dosing) is indicated for maintenance treatment following induction on a transmucosal buprenorphine-continuing product (not direct initiation).

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 presented two clinical case studies included in the submission and discussed the benefits of direct initiation with Buprenorphine Weekly, particularly for people in rural areas, such as avoiding adherence challenges during induction, removing the need to attend a pharmacy for daily dosing, and removing associated patient cost and travel burdens. The clinician noted that the

addition of Buvidal Monthly 160 mg would allow clinicians to provide improved treatment and safely and effectively manage patients requiring sublingual buprenorphine with a dosing range of 26-32 mg. The clinician noted inequity in patient cost for the current section 100 listing, as 89% of dosing points are community pharmacies, where patients are required to pay unregulated and uncapped private costs to pharmacies for their dosing. The clinician discussed that a section 85 listing would ensure adequate pharmacist remuneration, with patient costs capped and captured within the safety net, ensuring equal access for these medications regardless of the treatment or dosing setting. The PBAC had no further questions for the clinician. The PBAC noted that the clinician contributed to the main submission and restated information that was already included in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website.
- 6.3 A comment from Better Access Australia advocated for an end to ‘the charging of uncapped fees that do not count towards a patient’s Safety Net’. The organisation proposed that making ODT medicines dual Section 85/100 listed would ‘end the discriminatory practice of current s100 uncapped fees’. The organisation stated that delays to the dual listing on the basis of a Post-market Review (PMR) being in train would be ‘unfair to patients.’ The PBAC noted that the dual listing would not prevent pharmacies charging additional fees.

Clinical studies

- 6.4 The submission was based on:
- Two studies of prolonged-release buprenorphine presented in the November 2018 and March 2019 submissions:
 - One double-blind randomised trial (HS-11-421) comparing prolonged release buprenorphine with sublingual buprenorphine/naloxone in untreated patients with moderate to severe opioid use disorder.
 - One single arm open-label study (HS-14-499) of prolonged release buprenorphine assessing safety and tolerability in patients with moderate to severe opioid use disorder taking sublingual buprenorphine or sublingual buprenorphine/naloxone, or actively seeking treatment.
 - Two additional studies that have been completed subsequent to PBAC initial considerations of prolonged release buprenorphine:
 - One open-label randomised trial (HS-17-585) comparing prolonged release buprenorphine with sublingual buprenorphine or sublingual buprenorphine/naloxone in patients with moderate to severe opioid use disorder or opioid dependence.
 - One open-label non-randomised study (dBC2531) in patients in correctional centres with moderate to severe opioid use disorder comparing prolonged

release buprenorphine in patients previously not receiving opioid agonist treatment, with oral methadone in patients already stable on treatment.

6.5 At the time of submission, a study report for dBC2531 had not been published, however, at the time of evaluation, the results of the study had been published (Dunlop et al, 2021).

6.6 Details of the studies presented in the submission are provided in the table below.

Table 1: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HS-11-421	A phase III, randomised, 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. 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.	April 2018 JAMA Internal Medicine 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. Frost M, Bailey GL, Lintzeris N, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult outpatients with opioid use disorder.	June 2017 Addiction 2019; 114(8): 1416-1426
HS-15-585	A phase II, open-label, partially randomised, three treatment group, multi-site study assessing pharmacokinetics after administration of the once weekly and once monthly, long-acting, subcutaneous injectable depot of buprenorphine (CAM2038) at different injection sites in opioid dependent subjects with chronic pain	Not reported.
HS-17-585 (DEBUT)	A randomized, open-label, active-comparator, multi-center trial comparing a once-weekly and once-monthly long-acting subcutaneous injectable depot of buprenorphine (CAM2038) to buprenorphine standard of care in adult outpatients with opioid dependence. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-reported outcomes of treatment of opioid dependence with weekly and monthly subcutaneous depot vs daily sublingual buprenorphine: a randomized clinical trial.	May 2020 JAMA Network Open 2021; 4(5):e219041
dBC2531 (UNLOC-T)	Assessing the safety and feasibility of long-acting depot of buprenorphine in adults requiring treatment for opioid use disorder in NSW custodial settings (protocol). <i>Dunlop AJ, White B, Roberts J, et al. Treatment of opioid dependence with depot buprenorphine (CAM2038) in custodial settings.</i>	November 2019 <i>Addiction 2021; epub ahead of print</i>

Source: Constructed during the evaluation

Italicised study was identified during the evaluation.

Patients from HS-15-549 were included in pooled demographic data for the 160 mg formulation but did not contribute efficacy or safety data to the submission and were not considered further during the evaluation.

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

Table 2: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
HS-11-421	428	Randomised, double-blind, active controlled, multicentre study; 24 weeks	Low	Adults with moderate-severe OUD with no OST in the past 60 days	% urine samples negative for illicit opioids, time to sustained abstinence, retention, safety
HS-14-499	227	Single arm, open label, multicentre, international study; 48 weeks	High	Adults with moderate-severe OUD, seeking treatment or on SL BPN	Safety, % urine samples negative for illicit opioids, quality of life
HS-17-585	120	Randomised, open-label, active controlled, multicentre study; 24 weeks	High	Adults with moderate-severe OUD, seeking treatment or on SL BPN ¹	Patient reported outcomes, % urine samples negative for illicit opioids, safety
dBC2531	129	Non-randomised, active controlled, open label study; 16 weeks	High	Adult prisoners with moderate-severe OUD, seeking treatment or on methadone	Safety, retention, self-reported non-prescribed opioid use, patient reported outcomes

Source: November 2018 PBAC meeting; Table 24, pp51-52; Table 26, pp56-57; Table 28, pp59-61; Table 29, pp62-63 of the submission. Abbreviations: BPN, buprenorphine; OST, opioid substitution therapy; OUD, opioid use disorder; SL, sublingual.

¹ All of the participants enrolled in HS-17-585 were receiving sublingual buprenorphine or sublingual buprenorphine/naloxone at study entry; although the study allowed patients who were not currently receiving treatment.

- 6.8 The submission did not present any differences between the study settings and the proposed Australian PBS setting/population. However, the additional evidence provided in the submission, not previously considered by the PBAC, HS-17-585 and dBC2531 were both conducted in Australia.
- 6.9 Recent Australian treatment guidelines recommend direct initiation onto the weekly formulation of prolonged release buprenorphine, consistent with the updated product information (Lintzeris 2019 NSW Clinical guidelines for use of depot in the treatment of opioid dependence; Lintzeris 2020 Interim guidance for the delivery of medication assisted treatment of opioid dependence in response to COVID-19: a national response). However, the requested restriction would also allow patients to be directly initiated onto the monthly formulation, which is inconsistent with the TGA indication and Australian treatment Guidelines.
- 6.10 Expert opinion provided in a letter to the TGA in support of listing the 160 mg monthly dose stated that there was a role for this dosage strength in clinical practice in Australia. The letter stated that this dose may need to be prescribed for approximately 10-15% of patients on monthly doses who do not respond adequately to lower monthly doses. The clinical characteristics of the patient group likely to require a higher dose includes patients with higher than average neuroadaptation to opioids and/or with higher than typical access to illicit opioids (for example, people engaged in sex work; some people in custody). The advice stated that the availability of a 160 mg monthly dose adds to the clinical response for treatment-resistant patients and other complex patients (Attachment 1 to the submission: Investigator statement to TGA 10 March 2020).

Comparative effectiveness

Efficacy data supporting direct initiation and maintenance treatment with prolonged release buprenorphine

6.11 Table 3 summarises the key efficacy outcomes in HS-11-421, the key trial considered by the PBAC at its November 2018 and March 2019 meetings. Patients in trial HS-11-421 had received no medication assisted treatment for opioid use disorder within 60 days of randomisation and were directly initiated onto their randomised treatment (sublingual buprenorphine/naloxone or prolonged release buprenorphine) after a test dose of open-label 4 mg sublingual buprenorphine/naloxone to assess tolerability.

Table 3: Summary of key efficacy outcomes in HS-11-421 (ITT population)

Outcome	Prolonged release BPN (N=213)	Sublingual BPN/NX (N=215)	Treatment difference (95% CI)	p-value
Primary outcomes				
n (%) responders ¹	37 (17.4%)	31 (14.4%)	3.0 (-4.0, 9.9)	0.001 (non-inferiority)
% opioid-negative urine samples, LS mean (SD)	35.1 (36.00)	28.4 (36.46)	6.7 (-0.1, 13.6)	<0.001 (non-inferiority)
Secondary outcomes				
% opioid-negative urine samples, with self-report, CDF Week 5-25				
- Mean (SD)	35.1 (37.17)	26.7 (37.15)	-	0.004
- Median (range)	26.7 (0-100)	0 (0-100)	-	
% opioid-negative urine samples, without self-report, CDF Week 5-25				
- Mean (SD)	35.8 (37.41)	27.7 (37.40)	-	0.008
- Median (range)	26.7 (0-100)	6.7 (0-100)	-	
Time to sustained abstinence of opioid use				
- n (%) with sustained abstinence	39 (18.3%)	30 (14.0%)	-	0.221
- Median time to event	Not reached	Not reached	-	
Retention rate, n (%)	121 (56.8%)	126 (58.6%)	-1.8 (-11.2, 7.6)	0.006 (non-inferiority)

Source: Table 17, p25 of the submission

Abbreviations: BPN, buprenorphine; CDF, cumulative distribution function; CI, confidence interval; LS, least squares; NX, naloxone; SD, standard deviation

¹ A responder was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24).

6.12 In November 2018, the PBAC considered that the results of Trial HS-11-421 showed no significant difference in efficacy for prolonged release buprenorphine 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 (para 7.4, Buprenorphine PSD, November 2018 PBAC meeting).

6.13 In November 2018, the PBAC considered that, despite a statistically significant benefit of prolonged release buprenorphine over sublingual buprenorphine/naloxone for the cumulative distribution function of proportion of negative urine samples, the measure was difficult to interpret and was of unclear clinical importance, and was therefore not sufficient to support a claim of superior efficacy given all other clinical measures demonstrated non-inferiority (para 7.5, Buprenorphine PSD, November 2018 PBAC meeting).

- 6.14 An analysis of the proportion of subjects with negative urine samples by time point showed that, in both treatment arms, approximately 29% of subjects had no evidence of illicit opioid use by Week 2, which increased to a maximum of 40.8% at Week 10 in the prolonged release buprenorphine arm, and to 31.6% at Week 8 in the sublingual buprenorphine/naloxone arm.
- 6.15 HS-14-499, the long-term single-arm safety study considered by the PBAC at its November 2018 and March 2019 meetings, presented results for the overall population, as well as subgroups newly initiating prolonged release buprenorphine or switching to prolonged release buprenorphine from sublingual buprenorphine. Subjects who were receiving sublingual buprenorphine at study entry and switched to prolonged release buprenorphine had a high percentage of negative urine samples from Month 1 (72.8%) through to Month 12 (78.3%; range: 75.0% to 83.6%). Subjects who were new to buprenorphine treatment had a low percentage of negative urine samples at Month 1 (2.7%), which increased through to Month 12 (48.3%; range: 22.9% to 48.3%).
- 6.16 Table 4 summarises the key efficacy outcomes in study dBC2531, an open-label, non-randomised study of patients with opioid use disorder in custody in New South Wales. Patients who were not in opioid agonist treatment at recruitment commenced on prolonged release buprenorphine, and patients already stable on oral methadone treatment were recruited to the comparator arm and continued on methadone. Study dBC2531 has not been considered by the PBAC previously.
- 6.17 In study dBC2531, illicit drug use was measured by self-report, rather than urine toxicology. In the study publication (Dunlop 2021), it is noted that self-report was used to monitor drug use to address patient confidentiality concerns in custodial settings, noting that self-reported drug use is generally valid, particularly when independent of treatment process or potential adverse consequences. Custodial settings often employ urine drug screening to monitor drug use in prisons with sanctions (e.g. loss of visits or other punishments) when positive drug tests are returned, making it unlikely that a participant who is likely to yield a positive result would voluntarily submit to this testing.

Table 4: Summary of key efficacy outcomes in dBC2531 (ITT population)

Outcome	Prolonged release BPN (N=67)	Oral methadone (N=62)
Self-reported non-prescribed opioid use; n (%)		
Baseline	65 (97.0%)	1 (1.6%)
4 weeks	41 (61.2%)	1 (1.6%)
16 weeks	8 (12.3%)	0 (0%)
Change from baseline to 4 weeks; OR (95% CI)	0.048 (0.010, 0.221)	NR
Change from baseline to 16 weeks; OR (95% CI)	0.0035 (0.001, 0.018)	NR
Self-reported days of non-prescribed opioid use; mean (SD)		
Baseline	22.51 (9.67)	0.02 (0.13)
4 weeks	5.41 (7.70)	0.02 (0.13)
16 weeks	2.14 (6.61)	0.00 (0.00)
Change from baseline to 4 weeks; CCR (95% CI)	0.35 (0.26, 0.48)	NR
Change from 4 weeks to 16 weeks; CCR (95% CI)	0.67 (0.39, 1.17)	NR

Source: Table 4, p6 Dunlop 2021

Abbreviations: BPN, buprenorphine; CCR, conditional count ratio; NR, not reported

6.18 The prevalence of self-reported non-prescribed opioid use in the prolonged release buprenorphine arm statistically significantly decreased between baseline (97%) and week 4 (61%; OR 0.048, 95% CI 0.010, 0.221) and week 16 (12%; OR 0.0035, 95% CI 0.0007, 0.018). The frequency of self-reported non-prescribed opioid use also decreased statistically significantly between baseline and week 4 (22.51 to 5.41 days; conditional count ratio (CCR) 0.35, 95% CI 0.26, 0.48), but not between weeks 4 and 16 (5.41 to 2.14 days; CCR 0.67, 95% CI 0.39, 1.17). Among methadone patients, the prevalence of non-prescribed opioid use was low at baseline (1.6%) and remained low at weeks 4 (1.6%) and 16 (0%). Retention in treatment for patients receiving prolonged release buprenorphine was 92.3%.

New efficacy data supporting maintenance treatment with prolonged release buprenorphine

6.19 HS-17-585 was a randomised, open-label, multicentre (6 Australian sites) trial conducted under naturalistic conditions to compare patient reported outcomes associated with prolonged release buprenorphine versus sublingual buprenorphine standard of care in adult patients with opioid use disorder. None of the participants in HS-17-585 were directly initiated on prolonged release buprenorphine, although this was allowed according to the trial protocol. Trial HS-17-585 has not been considered by the PBAC previously.

6.20 In trial HS-17-585, there were no statistically significant differences in illicit opioid use between prolonged release buprenorphine and sublingual buprenorphine standard of care treatment arms at any time point. The primary outcome of the trial, mean Treatment Satisfaction Questionnaire for Medication global satisfaction score, was significantly higher for the prolonged release buprenorphine arm compared with the sublingual buprenorphine arm at week 24. Improved outcomes for patients treated with prolonged release buprenorphine were also observed for several secondary patient reported outcomes.

Efficacy data supporting the 160 mg monthly dose of prolonged release buprenorphine

- 6.21 No formal analysis of efficacy data was presented in the submission in support of the treatment benefit of the 160 mg monthly dose of prolonged release buprenorphine.
- 6.22 The submission instead presented subgroup analyses of trial HS-11-421 excluding patients who received either the 160 mg monthly dose of prolonged release buprenorphine or the 32 mg daily dose of sublingual buprenorphine/naloxone (the 32 mg sublingual buprenorphine/naloxone dose was included in HS-11-421 as a reference product dose corresponding to 160 mg monthly prolonged release buprenorphine in those cases where higher doses were needed). Results for the complement subgroup who received 160 mg monthly prolonged release buprenorphine or 32 mg daily sublingual buprenorphine/naloxone were not presented, although the numbers of patients were small (9 in each arm).
- 6.23 The results for the subgroup analyses excluding patients who received 160 mg monthly prolonged release buprenorphine or 32 mg sublingual buprenorphine/naloxone were similar to those for the ITT population for both outcomes. These results were not unexpected given the small number of patients who received 160 mg monthly prolonged release buprenorphine (N=9) or 32 mg daily sublingual buprenorphine/naloxone (N=9).
- 6.24 In a letter to the TGA to support the addition of the 160 mg dose of prolonged release buprenorphine, the chief investigator of study dBC2531 stated that a clinical benefit was noted for the patients prescribed the 160 mg dose in the study (Attachment 1 to the submission: Investigator statement to TGA 10 March 2020). However, the dBC2531 study publication (Dunlop 2021) does not present efficacy data by dose. As seen in Table 4 above, the ESC noted that the results for dBC2531 showed a significant reduction in self-reported non-prescribed opioid use. The ESC also noted that 40% of patients in dBC2531 received the 160 mg monthly dose.

Comparative harms

Safety data supporting direct initiation with prolonged release buprenorphine

- 6.25 In trial HS-11-421, previously considered by the PBAC, patients had received no medication assisted treatment for opioid use disorder within 60 days of randomisation, and were directly initiated onto their randomised treatment. The incidence of adverse events in the prolonged release buprenorphine arm (60%) was slightly higher than the incidence of adverse events in the sublingual buprenorphine/naloxone arm (55%), with similar proportions of patients experiencing drug-related adverse events (33% versus 30%). The most common adverse events in the prolonged release buprenorphine arm were injection site pain (8.9%), headache (7.5%), constipation (7.5%), nausea (7.0%), and injection site pruritis (6.1%). Incidences of individual adverse events not related to injection site were generally

comparable between prolonged release buprenorphine and sublingual buprenorphine/naloxone arms.

- 6.26 In the HS-14-499 study, previously considered by the PBAC, 37 (16.3%) patients had received no medication assisted treatment for opioid use disorder within 60 days of study entry and were directly initiated onto prolonged release buprenorphine, and 190 (83.7%) were receiving sublingual buprenorphine at study entry and were switched to prolonged release buprenorphine. The most common adverse events were injection site pain (15.4%), injection site swelling (11.9%), injection site erythema (9.3%), headache (7.9%), and nasopharyngitis (7.9%). The incidence of adverse events was higher in subjects who were switched to (69.0%) versus those who were initiated on (32.4%) prolonged release buprenorphine.
- 6.27 Table 5 summarises the adverse events in the dBC2531 study, which has not been considered by the PBAC previously. Patients in the prolonged release buprenorphine arm were not receiving opioid agonist treatment at recruitment and were directly initiated onto prolonged release buprenorphine. Adverse events were not reported for the oral methadone arm.

Table 5: Summary of adverse events in the prolonged release buprenorphine arm of dBC2531; n (%)

Category	Prolonged release BPN (N=67)
Any adverse event	65 (97%)
Drug-related adverse event	63 (94%)
Injection site adverse event (≥2 mild or ≥1 moderate)	15 (22%)
Non-injection site adverse event	56 (84%)
Severe adverse event	1 (2%)
Death	0
Serious adverse event	2 (3%)
Hospitalisation due to serious adverse event	2 (3%)
Drug-related serious adverse event	0
Drug overdose	0
Discontinued study drug due to a drug-related adverse event	4 (6%)
Adverse events occurring in ≥10% of subjects	
Injection-site pain	35 (52%)
Constipation	34 (51%)
Injection site swelling*	23 (34%)
Headache	19 (28%)
Injection site erythema	15 (22%)
Nausea	14 (21%)
Vomiting	13 (19%)
Self-reported sedation	10 (15%)
Self-reported urinary hesitancy	10 (15%)
Pruritis	7 (10%)
Rash	7 (10%)

Source: Tables 2 and 3, p5 Dunlop 2021

Abbreviations: BPN, buprenorphine

*Includes injection site mass and induration

- 6.28 The most common adverse events in the study were consistent with those in HS-11-421 and HS-14-499, however the incidence of individual adverse events was generally higher in dBC2531 compared with HS-11-421 and HS-14-499. The most common

adverse events were injection site pain (52%), constipation (51%), injection site swelling (34%), headache (28%), and injection site erythema (22%).

Safety data supporting the 160 mg monthly dose of prolonged release buprenorphine

- 6.29 Prolonged release buprenorphine adverse event data by dose have not been considered by the PBAC previously.
- 6.30 Analyses of adverse events by dose in trial HS-11-421 and adverse events by dose in HS-11-421 and HS-14-499 combined (see Table 13, p17 of the submission) show a trend of increasing incidence of adverse events with increasing doses of weekly prolonged release buprenorphine, but no dose response pattern with monthly prolonged release buprenorphine. The submission suggested that the different patterns between weekly and monthly dosing regimens are likely due to the higher frequency of visits, higher total number of injections and larger injection volume associated with weekly versus monthly dosing.
- 6.31 Nine (4.2%) of the 213 subjects in the prolonged release buprenorphine arm of trial HS-11-421 and 22 (9.7%) of the 227 subjects receiving prolonged release buprenorphine in study HS-14-499 were exposed to at least one dose of the 160 mg monthly formulation. Of the 31 patients who received 160 mg prolonged release buprenorphine in HS-11-421 and HS-14-499, 16 (51.6%) experienced at least one adverse event, one patient (3.2%) experienced a serious adverse event, and there were no deaths or adverse events leading to withdrawal.
- 6.32 Table 6 compares safety outcomes from the safety population of trial HS-17-585 and subjects in the trial who received at least one dose of 160 mg monthly prolonged release buprenorphine.

Table 6: Summary of treatment emergent adverse events in HS-17-585; n (%)

Category	Safety population		Subgroup receiving 160 mg prolonged release BPN (N=13)
	Prolonged release BPN (N=60)	Sublingual BPN SOC (N=59)	
Any adverse event	54 (90.0%)	49 (83.1%)	9 (69.2%)
Drug-related adverse event	39 (65.0%)	12 (20.3%)	6 (46.2%)
Injection site pain	11 (18.3%)	0 (0%)	1 (7.7%)
Injection site mass	10 (16.7%)	0 (0%)	2 (15.4%)
Injection site bruising	5 (8.3%)	0 (0%)	0 (0%)
Injection site erythema	3 (5.0%)	0 (0%)	0 (0%)
Injection site vesicles	1 (1.7%)	0 (0%)	1 (7.7%)
Serious adverse event	9 (15.0%)	9 (15.3%)	1 (7.7%)
Drug-related serious adverse event	1 (1.7%)	0 (0%)	1 (7.7%)
Discontinued study drug due to an adverse event	0 (0%)	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)

Source: Table 15, p19 of the submission

Abbreviations: BPN, buprenorphine; SOC, standard of care

- 6.33 In trial HS-17-585, 13 (21.7%) of the 60 subjects in the prolonged release buprenorphine arm were exposed to at least one dose of the 160 mg monthly

formulation. Nine (69.2%) of the 13 patients receiving at least one dose of the 160 mg formulation experienced at least one adverse event, with six patients (46.2%) experiencing treatment-related adverse events. Adverse events that were reported by more than one patient receiving 160 mg monthly prolonged release buprenorphine were injection site mass (reported by 2 patients) and lower respiratory tract infection (reported by 2 patients).

- 6.34 In study dBC2531, 27 (40.3%) of the 67 subjects in the prolonged release buprenorphine arm were exposed to at least one dose of the 160 mg monthly formulation. The study publication (Dunlop 2021) does not report adverse events by dose, however, in a statement to the TGA, the study's chief investigator noted that a higher prevalence of side effects was not seen in the group administered 160 mg monthly prolonged release buprenorphine doses compared to other weekly or monthly doses (Attachment 1 to the submission: Investigator statement to TGA 10 March 2020).

Benefits/harms

- 6.35 A benefits/harms summary was not presented due to the previously accepted claim of non-inferiority of prolonged release buprenorphine to sublingual buprenorphine/naloxone (para 7.8, Buprenorphine PSD, November 2018 PBAC meeting; para 7.4, Buprenorphine PSD, March 2019 PBAC meeting).

Clinical claim

- 6.36 No formal clinical claim was made in the submission. The PBAC previously accepted a claim of non-inferiority of prolonged release buprenorphine to sublingual buprenorphine/naloxone (para 7.8, Buprenorphine PSD, November 2018 PBAC meeting; para 7.4, Buprenorphine PSD, March 2019 PBAC meeting). The cost minimisation analysis of prolonged release buprenorphine versus sublingual buprenorphine/naloxone presented in the current submission is consistent with a claim of non-inferiority.
- 6.37 The data presented in the submission to support the proposed changes to the restriction (adding the 160 mg monthly dose; allowing direct initiation) were based on the evidence submitted to the TGA to support the recently approved changes to the prolonged release buprenorphine restriction and product information.
- 6.38 Evidence of the efficacy and safety of direct initiation with the weekly formulation of prolonged release buprenorphine compared with sublingual buprenorphine/naloxone was based on the evidence previously considered by the PBAC (HS-11-421, HS-14-499), as well as additional evidence from study dBC2531, conducted in patients in custodial settings in New South Wales. In November 2018, the PBAC considered that the evidence from HS-11-421 and HS-14-499 supported a claim of non-inferior efficacy and safety of prolonged release buprenorphine compared to sublingual buprenorphine/naloxone (para 7.8, Buprenorphine PSD, November 2018 PBAC meeting). Additional evidence presented in the submission from study dBC2531 is

consistent with non-inferior efficacy and safety. The ESC considered that the available evidence supported direct initiation with the weekly formulation of prolonged release buprenorphine.

- 6.39 No efficacy data were provided for the use of the 160 mg monthly dose of prolonged release buprenorphine. However, evidence previously considered by the PBAC from HS-11-421 and HS-14-499 included patients receiving this dose strength, and analysis of the HS-11-421 study data for key outcomes, excluding data from patients receiving the 160 mg dose strength, showed no difference in treatment effect to the ITT population. The ESC noted that safety data were presented from studies HS-11-421, HS-14-499 and HS-17-585 for the subgroup of patients who received the 160 mg monthly dose, with results indicating similar proportions of adverse events compared to the ITT populations, and no evidence of a dose response pattern with the monthly formulation. The ESC considered that new data from study dBC2531, in which 40% of patients received 160 mg monthly, supported the efficacy of the higher dose strength. On balance, the ESC was supportive of the request to list the 160 mg monthly dose (noting that the sponsor proposed the same price as the other monthly formulations).

Economic analysis

- 6.40 The submission presented a cost minimisation analysis of prolonged release buprenorphine based on the previously accepted claim of non-inferior efficacy and safety compared to sublingual buprenorphine/naloxone (para 7.8, Buprenorphine PSD, November 2018 PBAC meeting; para 7.4, Buprenorphine PSD, March 2019 PBAC meeting).
- 6.41 At the March 2019 meeting the PBAC recommended prolonged release buprenorphine on a cost minimisation basis versus sublingual buprenorphine/naloxone, and noted that cost effectiveness was acceptable based on drug costs alone, flat priced on a per day basis across dose strengths, at an equi-effective dose of 18.34 mg/day of sublingual buprenorphine/naloxone, with a [REDACTED] % price premium (para 7.1 and 7.5, Buprenorphine PSD, March 2019 PBAC meeting). The PBAC considered that the MBS prescribing and administration costs included in the cost minimisation analysis 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 (para 7.5, Buprenorphine PSD, March 2019 PBAC meeting).
- 6.42 The estimated equi-effective doses used in the submission were unchanged from those accepted by the PBAC at the March 2019 meeting (para 7.2, Buprenorphine PSD, March 2019 PBAC meeting).
- Prolonged release buprenorphine 50 mg/mL weekly and 356 mg/mL monthly are equivalent to 18.34 mg sublingual buprenorphine/naloxone daily.
- 6.43 The calculated cost per day of sublingual buprenorphine/naloxone (\$ [REDACTED]) was based on the equi-effective doses, and was unchanged from the March 2019 minor resubmission.

6.44 Table 7 summarises the non-drug costs included in the cost minimisation analysis, with costs and frequency of services informed by responses from a sponsor survey of OST service providers (prescribers: n=28, and pharmacists: n=11).

Table 7: Non-drug costs included in the cost minimisation analysis

Component	Units per 28 days			Costs per 28 days		
	PR BPN q1w	PR BPN q4w	SL BPN/NX	Weighted PR BPN ^a (\$)	SL BPN/NX (\$)	Difference (\$)
GP visits for prescribing/monitoring (\$39.10/visit; MBS 23; Survey Q.18, 23, 24)	█	█	█	█	█	█
Administration of drug, supervision PR BPN (\$17.90 per visit; MBS item 3) SL BPN/NX (\$█ per day; Survey Q.9,10)	█	█	█	█	█	█
Pharmacy handling and storage PR BPN weekly (\$█ disp.; Survey Q.12) PR BPN monthly (\$█ disp.; Survey Q.13)	█	█	█	█	█	█
Total non-drug cost per 28 days				█	█	█
Cost savings of PR BPN (difference in non-drug costs / 28)						█

Source: Table 20, p40 of the submission

Abbreviations: BPN, buprenorphine; GP, general practitioner; MBS, Medical Benefits Schedule; NX, naloxone; PR, prolonged release; q1w, once weekly; q4w, once every 4 weeks; SL, sublingual

^a Based on HS-14-499 study: 56% (128/227) of patients stabilised on monthly dosing regimen by end of study, and 75% retained on treatment. Therefore assumed 74.7% (56/75) on monthly dosing and remainder (25.3%) weekly dosing

6.45 The non-drug cost saving of \$█/day in the current submission was the same as that derived in the March 2019 submission, despite differences in the estimated non-drug cost components for sublingual and prolonged release buprenorphine.

6.46 Key differences in included costs, between the cost minimisation analyses include:

- Higher GP prescribing costs due to an increase in the MBS item 23 (level B GP consultation) fee and updated estimates of the number of GP visits per 28 day period for sublingual and prolonged release buprenorphine, based on the results of the sponsor OST survey.
- A reduction in the private patient service/dispensing fees for prolonged release buprenorphine, based on the results of the sponsor OST survey.
- The assumption that there will be no delivery fees for prolonged release buprenorphine (compared with \$█ per dispensing in the March 2019 submission). This was based on the results of the sponsor survey, which indicated that usual medication delivery channels for Schedule 8 drugs are used and there are no additional costs or fees charged.
- A small increase in GP administration costs associated with prolonged release buprenorphine due to an increase in the MBS item 3 (level A GP consultation) fee.
- A reduction in the supervision costs associated with sublingual buprenorphine/naloxone, based on the cost in the private setting (derived from the sponsor OST survey, compared to a published estimate in the March 2019 submission). The costs associated with supervision in the public setting were unchanged, as was the distribution of use in the private and public settings.

- 6.47 The submission acknowledged that relatively small samples contributed to estimates based on the sponsor OST survey, but suggested that the variation in responses reflects the inconsistencies in fees charged across service providers and jurisdictions. Notwithstanding the real world variation reflected in the survey responses, the estimated service fees derived from the survey are highly uncertain, and may not reflect fees associated with the service models that have been established since prolonged release buprenorphine was listed on the PBS. The PSCR claimed that the survey results are consistent with other reports of the costs of supervised dosing (Chalmers 2009 and Feyer 2008), and that the proposed savings are plausible in magnitude.
- 6.48 The cost minimisation analysis included private patient fees, which the PBAC has previously considered to be inappropriate to include in the cost minimisation analysis (para 7.5, Buprenorphine PSD, March 2019 PBAC meeting).
- 6.49 Table 8 summarises the results of the cost minimisation analysis.

Table 8: Cost minimisation analysis of prolonged release buprenorphine versus sublingual buprenorphine/naloxone

Component	Current submission (\$)	Source / method
SL BPN/NX cost per day (AEMP)	██████	Steady state mean dose of SL BPN/NX 18.34 mg/day (HS-11-421 trial); relative use of 8/2 mg (PBS 9749D) and 2/0.5 mg (PBS 9750E) SL BPN/NX (2017 IMS data)
Price premium	██████	██████% of SL BPN/NX equivalent cost per day (\$██████ × 0.██████)
Service model cost savings per day	██████	Cost savings from a community pharmacy model of PR BPN vs SL BPN/NX (\$██████/28 days)
Price of PR BPN per day (AEMP)	██████	(\$██████ + \$██████ + \$██████).
Price of PR BPN for 28 days (AEMP)	██████	Cost per day (\$██████ × 28)

Source: Table 19, p38 of the submission

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

- 6.50 Despite the differences in non-drug costs associated with the prescribing, dispensing and administration of prolonged release buprenorphine, the cost minimisation analysis estimated the price of prolonged release buprenorphine to be unchanged from the March 2019 minor resubmission (i.e. \$██████ per day). The estimated price per day is higher than the current cost per day of prolonged release buprenorphine on the PBS (\$13.20 per day), as it includes non-drug costs (\$██████) related to MBS prescribing and administration as well as private patient fees, claimed to be consistent with the emerging practice model. The ESC considered non-drug costs would be informed by the current ODTP Post-market Review, which will consider service delivery arrangements.
- 6.51 The PSCR argued for including private fees in support of the \$██████/day price increase, on the basis that it is modest, and that the PBAC’s preferred perspective per its guidelines includes any costs to patients. Overall, the ESC agreed with the evaluation that the data informing the service model savings are associated with considerable uncertainty and include private patient fees the PBAC has previously considered to be inappropriate to include in the cost minimisation analysis. The Pre-PBAC Response

requested clarification from the PBAC regarding whether private fees are considered inappropriate in a CMA, or whether it is the uncertainty in the measurement of these fees that makes them inappropriate for inclusion.

Drug cost/patient/year

- 6.52 The drug cost per patient per year, based on the proposed price and a Section 100 listing, is \$ [REDACTED] (= \$ [REDACTED]/day based on the AEMP×365 days). This is unchanged from the March 2019 resubmission.
- 6.53 The drug cost per patient per year, based on the proposed price and a Section 85 listing, is \$ [REDACTED] (= \$ [REDACTED] DPMQ for the weekly dose/7 days×365 days per year×25.3%+\$ [REDACTED] DPMQ for the monthly (four-weekly) dose/28 days×365 days per year×74.7%) based on the distribution between dose formulations used in the budget impact model.
- 6.54 The submission did not estimate the proportions of use between Schedules under a dual Section 100 (ODTP)/Section 85 listing.

Estimated PBS usage & financial implications

- 6.55 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation of prolonged release buprenorphine for the treatment of opioid use disorder (OUD) over the first six years of listing, similar to the approach used in the March 2019 submission. The estimated financial implications did not follow the recommended Utilisation and Cost Model Workbook template.
- 6.56 The estimated financial implications compare the impact of the proposed listing changes to the current listing of prolonged release buprenorphine on the PBS using three scenarios:
- Scenario one comparing the costs associated with a Section 100 listing at the higher proposed price to the current PBS Section 100 listing and price (no mark-ups, fees, or patient copayments);
 - Scenario two comparing the costs associated with a Section 85 listing at the current price (including mark-ups, fees, and patient copayments) to the current PBS Section 100 listing and price (no mark-ups, fees, or patient copayments); and
 - Scenario three comparing the costs associated with a Section 85 listing at the higher proposed price (including mark-ups, fees, and patient copayments) to the current PBS Section 100 listing and price (no mark-ups, fees, or patient copayments).
- 6.57 The submission assumed that the proposed changes to the prolonged release buprenorphine restriction (the addition of a Section 85 listing, the addition of a 160 mg monthly dose, removal of the requirement for prior stabilisation on sublingual buprenorphine) would have no impact on the utilisation of prolonged release buprenorphine. This assumption was inconsistent with the benefits these changes are claimed to offer patients receiving or considering OST, and the ESC noted there are

additional patients who may benefit from the 160 mg dose (with 10-15% of patients estimated not to respond to existing strengths) (see paragraph 6.7).

6.58 The submission did not estimate the financial implications of the proposed dual Section 100/Section 85 listing, with estimates provided based on all use under a Section 100 listing, or all use under a Section 85 listing. This does not reflect the proposed place in clinical practice in the submission. The PSCR stated that the approach used to estimate the impact of a Section 85 listing by assuming 100% uptake reflects the maximum possible (incremental) cost, or ‘worst case’ scenario.

6.59 Key inputs for the financial estimates are summarised in Table 9 below.

Table 9: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent patients receiving (OST) for OUD	Year 1: 53,667 to Year 6: 57,222 Linear projection of AIHW NOPSAD 2020 data (2012-2020) of patients receiving OST (methadone, SL BPN, SL BPN/NX).	NOPSAD 2020 data for PR BPN use were not included. The impact of COVID-19 on NOPSAD data was not considered. Estimates may be underestimated.
Prevalent untreated patients	Year 1: 43,113 to Year 6: 45,969 Assumed 44.5% of prevalent patients eligible for OST are untreated, based on an estimated 40,000 untreated patients in 2017 (MATOD 2018; Chalmers et al., 2009); (40,000 / [40,000 + total treated 2017])	Chalmers et al. (2009) used older data (2003-2007) to estimate patients previously treated but not continuing treatment, as a proxy for unmet need. Estimates predate changes to opioid prescribing and OTC opioid access (TGA, 2020). Estimates may be underestimated.
Distribution of OST use 2022-2027	Methadone: 58.2-54.5%; SL BPN: 4.5%; SL BPN/NX: 37.3-41.0% NOPSAD data 2008-2020, adjusted for assumed distribution of BPN therapies in NSW between SL BPN and SL BPN/NX, and methadone market change.	The assumed fixed proportion of SL BPN market at 4.5%, suggests all BPN market growth is in use of SL BPN/NX. This is not consistent with the NOPSAD data which showed more rapid market growth in SL BPN.
Uptake of PR BPN	█% of total OST market; PR BPN utilisation inflated by 25% for market growth in untreated population. Assumed. Uptake of █% of total OST market; with █% of uptake from methadone, and █% from SL BPN and SL BPN/NX	Uptake rates of PR BPN from methadone, sublingual buprenorphine and untreated patients are highly uncertain. Assumed 25% market growth was not related to numbers of untreated patients and was not adequately justified; this equates to 3.1% of the untreated market and may be underestimated.
Proportion of use between PR BPN formulations	q1w PR BPN: 25.3%; q4w PR BPN: 74.7% Based on use in HS-14-499 study: 56% (128/227) of patients stabilised on monthly dosing regimen by end of study, and 75% retained on treatment. Therefore assumed 74.7% (56/75) on monthly dosing and remainder (25.3%) weekly dosing.	The applicability of the dose distribution data from a clinical trial setting to the Australian setting is uncertain.
Patient copayment	\$20. Assumed	The submission acknowledged that the assumed copayment is most likely an overestimate.

Source: Section 5 of the submission; Buvidal_BIM updated_July 2021 spreadsheet

Abbreviations: BPN buprenorphine; NOPSAD, National Opioid Pharmacotherapy Statistics Annual; NX naloxone; OST, opioid substitution therapy; OUD, opioid use disorder; PR, prolonged release; q1w, once weekly; q4w, once every 4 weeks; SL, sublingual

6.60 The sources of data and methods used in the financial estimates were unchanged from the March 2019 minor submission, with the exception of updated utilisation data from the NOPSAD 2020 snapshot of OST medicine use.

6.61 Table 10 below presents the estimated use and financial implications of the proposed changes to the prolonged release buprenorphine PBS listing, over the first 6 years of listing.

Table 10: Estimation of the use and financial impact of PR BPN on the PBS

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Patients on treatment (NOPSAD data 2020)	53,666	54,377	55,089	55,800	56,511	57,221
Not treated (44.5% of total eligible population)	43,113	43,684	44,255	44,826	45,397	45,969
Total eligible population	96,779	98,061	99,344	100,626	101,908	103,190
PR BPN						
Uptake from treated patients (%)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
- Uptake from methadone (%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
- Uptake from SL BPN ^a (%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
- Uptake from SL BPN/NX ^a (%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Uptake from not treated ^b (additional █% of total PR BPN)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Patients treated with PR BPN	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Current Section 100 listing (AEMP), current price						
Current price, cost to PBS (AEMP \$13.20/day)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Scenario 1: Section 100 listing (AEMP), higher proposed price						
Proposed price, cost to PBS (AEMP \$█/day)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net difference in cost to PBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Scenario 2: Section 85 listing (DPMQ, excluding copayments), current price						
Current price, cost to PBS (DPMQ \$15.65/day ^a)	█ ³	█ ³	█ ³	█ ³	█ ⁵	█ ⁵
Patient copayment (\$█/script; weighted average \$█/day ^c)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Cost to PBS excl. copayment	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net difference in cost to PBS (excl. copayment)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Scenario 3: Section 85 listing (DPMQ, excluding copayments), higher proposed price						
Proposed price, cost to PBS (DPMQ \$█/day ^b)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Patient copayment (\$█/script; weighted average \$█/day ^c)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Cost to PBS excl. copayment	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net difference in cost to PBS (excl. copayment)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Buvidal_BIM updated_July 2021.xlsx

Abbreviations: AEMP, approved ex-manufacturer price; BPN, buprenorphine; NX, naloxone; OST, opioid substitution therapy; PR, prolonged release; q1w, once weekly; q4w, once every 4 weeks

^a Based on a DPMQ of \$116.24 for q1w and \$429.16 for q4w PR BPN; and relative use of 25.3% q1w/74.7% q4w from HS-14-499.

^b Based on a DPMQ of \$█ for q1w and \$█ for q4w PR BPN; and relative use of 25.3% q1w/74.7% q4w from HS-14-499.

^c Based on 4 scripts per 28 days of q1w and 1 script per 28 days of q4w PR BPN; and relative use of 25.3% q1w/74.7% q4w from HS-14-499.

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 500 to < 5,000

³ \$30 million to < \$40 million

⁴ \$0 to < \$10 million

⁵ \$40 million to < \$50 million

- 6.62 Based on a Section 100 listing at the higher proposed price, the submission estimated that the cost to the PBS of prolonged release buprenorphine was up to \$30 million to < \$40 million in Year 6, a total of \$200 million to < \$300 million over 6 years, with an incremental cost to the PBS of the proposed price increase of up to \$0 to < \$10 million in Year 6, a total of \$10 million to < \$20 million over 6 years.
- 6.63 Based on a Section 85 listing at the current PBS price, the submission estimated that the cost to the PBS of prolonged release buprenorphine was up to \$30 million to < \$40 million in Year 6, a total of \$200 million to < \$300 million over 6 years, with an incremental cost to the PBS of the proposed price increase of up to \$0 to < \$10 million in Year 6, a total of \$10 million to < \$20 million over 6 years.
- 6.64 Based on a Section 85 listing at the higher proposed price, the submission estimated that the cost to the PBS of prolonged release buprenorphine was up to \$40 million to < \$50 million in Year 6, a total of \$200 million to < \$300 million over 6 years, with an incremental cost to the PBS of the proposed price increase of up to \$0 to < \$10 million in Year 6, a total of \$30 million to < \$40 million over 6 years.
- 6.65 The submission estimated cost offsets from substituted OST medicines of up to 10 million to < \$20 million in Year 6, with total cost offsets over 6 years of \$80 million to < \$90 million. The cost offsets to the PBS of substituted OST medicines are the same across the current listing and proposed listing scenarios, and therefore do not affect the net financial implications.
- 6.66 The submission estimated the net costs to the MBS associated with the proposed listing compared to the current PBS listing, based on the costs of prescribing and administration estimated in the cost-minimisation analysis. However, the financial impact to the MBS is the same under the current listing scenario and the proposed listing scenarios, with no net costs to the MBS.
- 6.67 The ESC agreed with the evaluation that the estimated financial implications to the PBS of the proposed Section 85/Section 100 listing and price increase for prolonged release buprenorphine were uncertain for the following reasons:
- At the November 2018 and March 2019 meetings the PBAC considered the likely substitution from other OST could not be reliably determined until the practice model is known (para 7.9, Buprenorphine PSD, November 2018 PBAC meeting; para paragraph 6.16, Buprenorphine PSD, March 2019 PBAC meeting). Prolonged release buprenorphine has been listed on the PBS since September 2019 and several practice models have been established. However, estimates of uptake from the overall OST market and the proportions of uptake from other OST remain unchanged, and were not informed by prolonged release buprenorphine utilisation data from the NOPSAD 2020 snapshot data.
 - The assumed market growth of an additional 25% of uptake of prolonged release

buprenorphine was not adequately justified or directly related to the estimated numbers of untreated eligible patients. Given this represents approximately 3.1% of the estimated untreated population, the estimated market growth may be underestimated.

- While the submission acknowledged that the onset of the COVID-19 pandemic had, to some extent, precipitated the current submission to the PBAC, the impact of COVID-19 was not considered in the estimated utilisation of prolonged release buprenorphine in the Australian setting. The impact of COVID-19 on the updated NOPSAD snapshot 2020 data, and increased uptake of prolonged release buprenorphine in custodial and health services settings in Australia (Roberts 2021, Arunogiri 2021), may result in higher net costs to the PBS associated with the proposed changes in the submission.

6.68 The PSCR attempted to estimate the financial implications of a dual listing for a given uptake of Section 85 (ranging from 0-100%). The PSCR also estimated the potential impact of a Section 85 listing if it were to grow the size of the treated market by an additional 20-30% (see Table 11 below).

Table 11: Potential impact of a Section 85 listing if it grows the treated market by an additional 20-30%

Scenario	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
A: Status quo S100; Current price; 25% market growth	[Redacted] ¹	[Redacted] ¹	[Redacted] ¹	[Redacted] ²	[Redacted] ²	[Redacted] ²
B: Proposed scenario: S85; Proposed price; 30% market growth	[Redacted] ²	[Redacted] ²	[Redacted] ²	[Redacted] ²	[Redacted] ²	[Redacted] ²
Net impact	[Redacted] ³	[Redacted] ³	[Redacted] ³	[Redacted] ³	[Redacted] ³	[Redacted] ³

Source: PSCR

The redacted values correspond to the following ranges:

¹ \$10 million to < \$20 million

² \$20 million to < \$30 million

³ \$0 to < \$10 million

6.69 The ESC noted that the PSCR proposed scenario with a Section 85 listing at the proposed price, 30% market growth and 100% uptake would cost the PBS approximately \$1.5 million/year more than estimated in the submission (Scenario 3, Table 10). The Pre-PBAC Response noted the growth of 30% represented 300 more people treated, and those patients were more likely to be those unable to afford the unregulated fees currently. The PBAC noted lack of evidence for the claim of 300 currently untreated patients benefiting from listing.

6.70 The ESC noted that recent PBS data suggests there has been increasing uptake of long acting buprenorphine injections and consequently increasing expenditure. The ESC considered that this has implications for the robustness of the sponsor's financial

estimates (which were largely unchanged from estimates in previous submissions). The Pre-PBAC Response claimed the increasing expenditure and uptake noted by ESC supports, rather than compromises, the robustness of the revised estimates which include increasing expenditure and uptake.

- 6.71 The ESC considered that any revisions to the financial estimates would need to account for a mix of Section 85 and Section 100 (ODTP) utilisation as well as the potential market growth associated with a Section 85 listing.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of the new form, 160 mg monthly prolonged release buprenorphine, for the treatment of opiate dependence on the basis that it should be available only under special arrangements under Section 100 for opiate dependence with restricted benefit. The PBAC also recommended the change to the PBS restriction to remove the requirement for stabilisation on sublingual buprenorphine or sublingual buprenorphine/naloxone prior to commencing treatment with weekly prolonged release buprenorphine, consistent with the recent amendment to the TGA indication.
- 7.2 The listing of the 160 mg monthly injection form was recommended on a cost-minimisation basis to the other currently listed monthly forms of buprenorphine injection.
- 7.3 The PBAC did not recommend a price increase and did not make a decision for the consideration of the Section 85 (Restricted Benefit) listing in addition to the current Section 100 (ODTP). The PBAC noted the current Post-market Review of Opiate Dependence Treatment Program medicines (ODTP PMR), which is considering barriers to access including affordability of ODTP medicines. The PBAC considered that the request for dual Section 85/100 listing should be informed by the ODTP PMR. The sponsor may wish to resubmit to the PBAC concerning these matters after the outcomes of the ODTP PMR become available.
- 7.4 The PBAC noted the submission had proposed a restriction that would allow direct initiation on the monthly formulation of prolonged release buprenorphine, which is inconsistent with the TGA approved indication, which only allows direct initiation of the weekly and not the monthly formulation of prolonged release buprenorphine. The PSCR amended the proposed restriction for the monthly formulation to include the need to be stabilised on either the weekly formulation, sublingual buprenorphine, or sublingual buprenorphine/naloxone (whilst removing any reference to prior stabilisation for the weekly formulation). The PBAC agreed with the ESC that this was appropriate. The PBAC supported separate restrictions for the weekly and monthly formulations of prolonged release buprenorphine to provide for direct initiation of the weekly formulation and retention of the requirement for prior stabilisation for the monthly formulation.

- 7.5 The PBAC noted evidence previously considered by the PBAC (HS-11-421, HS-14-499), which supported a claim of non-inferior efficacy and safety of prolonged release buprenorphine compared to sublingual buprenorphine/naloxone (para 7.8, Buprenorphine PSD, November 2018 PBAC meeting). Additional evidence presented in the submission from study dBC2531, conducted in patients in custodial settings in New South Wales, was consistent with non-inferior efficacy and safety. The PBAC considered that the evidence supported direct initiation with the weekly formulation of prolonged release buprenorphine.
- 7.6 The PBAC noted evidence previously considered by the PBAC from HS-11-421 and HS-14-499 included patients receiving the 160 mg monthly dose of prolonged release buprenorphine, and analysis of the HS-11-421 study data for key outcomes, excluding data from patients receiving the 160 mg dose strength, showed no difference in treatment effect to the ITT population. The ESC noted that safety data were presented from studies HS-11-421, HS-14-499 and HS-17-585 for the subgroup of patients who received the 160 mg monthly dose, with results indicating similar proportions of adverse events compared to the ITT populations, and no evidence of a dose response pattern with the monthly formulation. The ESC considered that new data from study dBC2531, in which 40% of patients received 160 mg monthly, supported the efficacy of the higher dose strength. Overall, the PBAC supported the request to list the 160 mg monthly dose and considered the same flat price as the other monthly formulations was appropriate.
- 7.7 The PBAC noted that the submission claimed there would be a number of advantages of a Section 85 listing. For the claim of appropriate reimbursement for pharmacies and wholesalers for distribution, storage and dispensing, the PBAC noted that there may be costs to dispensers and wholesalers given the need to store and dispense these products and acknowledged that these costs are not currently being reimbursed through the Section 100 listing and in the private sector are recouped with private fees. For the claim of standardised patient fees instead of private, unregulated pharmacy-directed service fees, the PBAC noted that the survey of dispensers (n=11) indicated a Section 85 listing would not prevent charging of unregulated fees. For the claim of supply not being restricted to pharmacies approved for OST services, the PBAC considered this may not be reasonable given the current rate of pharmacy approval to provide ODTP (approximately 50%) and supply (nearly 90% of dosing). The PBAC considered that the matter of section 85 listing should be informed by the ODTP PMR.
- 7.8 The PBAC noted that submission argued for an increase in price from the previous cost-minimised price against sublingual buprenorphine/naloxone. The PBAC noted substantial uncertainty associated with the estimated practice model savings included in the cost minimisation analysis (CMA) due to private patient fees and the sponsor survey. The ESC noted that the inclusion of private patient fees was previously considered by the PBAC to be inappropriate. PBAC clarified that inclusion of private patient fees was inappropriate due to the substantial uncertainty associated with the

measurement of these fees. The ESC noted that estimates were informed by a sponsor survey with small numbers of responders and a wide range of responses. The Pre-PBAC response acknowledged the limitations of the sponsor survey, but argued that the savings are 'plausible – if not conservative'. PBAC disagreed, considering the evidence insufficient to support plausible savings, and advised that the revisions required to the economic evaluations were complex and should be informed by the PMR. Further, it was noted that Buprenorphine is not the only injectable buprenorphine product listed on the PBS and therefore sublingual buprenorphine/naloxone is not the only relevant comparator.

- 7.9 The PBAC noted some issues with the estimated financial implications. The PBAC noted that the submission claimed the addition of 160 mg strength would not affect utilisation. However, the ESC noted that additional patients (10-15% estimated not responding to existing strengths) would benefit from this higher strength. The PBAC agreed that listing of the 160 mg strength may increase utilisation, and thus expenditure, by up to 15%.
- 7.10 The PBAC noted the submission did not estimate the financial implications of the proposed dual Section 100/Section 85 listing, with estimates provided based on all use under a Section 100 listing, or all use under a Section 85 listing, thus not reflecting the proposed clinical place. The PSCR sought to address this by providing additional scenarios. The PBAC considered there was a lack of evidence in the submission and PSCR to support the utilisation and financial estimates of a Section 85 listing and the financial implications would best be informed by the PMR.
- 7.11 The PBAC reaffirmed its March 2019 advice that buprenorphine is not interchangeable with any other drugs or medicinal preparations on an individual patient basis, prolonged release buprenorphine is suitable for prescribing by nurse practitioners within a shared care model and the Early Supply Rule should apply.
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because monthly prolonged buprenorphine is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over sublingual buprenorphine/naloxone, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.13 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 and amend existing/recommended listing as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BUPRENORPHINE					
Buprenorphine 8 mg/0.16 mL modified release injection, 0.16 mL syringe	11759X	1	1	NA	Buvidal weekly
Buprenorphine 16 mg/0.32 mL modified release injection, 0.32 mL syringe	11774Q				
Buprenorphine 24 mg/0.48 mL modified release injection, 0.48 mL syringe	11773P				
Buprenorphine 32 mg/0.64 mL modified release injection, 0.64 mL syringe	11766G				
Restriction Summary 9213 / Treatment of Concept: 9212					
Section 100 – Opiate Dependence					
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					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					
Administrative Advice: Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.					
Administrative Advice: 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.					
Indication: Opiate dependence					
Treatment criteria:					
Must be treated by a health care professional					
AND					
Clinical criteria:					
The treatment must be within a framework of medical, social and psychological treatment					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
BUPRENORPHINE					
Buprenorphine 64 mg/0.18 mL modified release injection, 0.18 mL syringe	11754P	1	1	NA	Buvidal Monthly
Buprenorphine 96 mg/0.27 mL modified release injection, 0.27 mL syringe	11767H				
Buprenorphine 128 mg/0.36 mL modified release injection, 0.36 mL syringe	11768J				
Buprenorphine 160 mg/0.45 mL modified release injection, 0.45 mL syringe	NEW				
Restriction Summary 9213 / Treatment of Concept: 9212					
Section 100 – Opiate Dependence					
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					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					

	Administrative Advice: Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.
	Administrative Advice: 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.
	Indication: Opiate dependence
	Treatment criteria: Must be treated by a health care professional
	AND
	Clinical criteria: The treatment must be within a framework of medical, social and psychological treatment
	AND
	Clinical criteria: Patient must be stabilised on one of the following prior to commencing treatment with this drug for this condition: (i) weekly prolonged release buprenorphine (Buvidal Weekly) (ii) sublingual buprenorphine (iii) buprenorphine/naloxone

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Camurus are pleased the PBAC has given positive recommendations for the direct initiation and higher strength of Buvidal which will provide greater flexibility in the treatment for opioid dependence. Camurus thanks the PBAC for its continued acknowledgment of the access and compliance benefits of this innovative delivery mechanism for managing opioid dependence, reflecting the outcomes of the clinical trials conducted in Australia.

Opioid addiction is a disease where around only 1 in 3 trying to manage their opioid addiction are currently accessing any form of treatment on the opioid dependence treatment (ODT) program, and where around 3 lives are lost every day as a result of that untreated addiction. Multiple coronial reports and research papers have cited the affordability of the medicines as the barrier to access and continued treatment.

We remain disappointed the cost advantages of the Buvidal practice model relative to supervised dosing seem to be undervalued. Camurus notes that in 2018 the PBAC acknowledged that the private uncapped fees charged by pharmacy were a financial barrier to accessing treatment and that the listing of Buvidal with its reduced frequency of dosing may assist in making the treatments more affordable to patients and therefore improve access and uptake. Camurus notes that significant uncapped fees are being charged for access to Buvidal and other ODT Program products and that a s85 listing would preclude such charges and allow co-payments to be counted towards a patient's safety net. It is our expectation that given the volumes of dispensing occurring in the community pharmacy setting as cited by the PBAC and its subcommittees, the prevalence of s85 prescribing would see a significant diminution of s100 prescribing for access in the community setting retaining it only for the hospital, correctional and public clinic based setting, where it is our experience such private fees are not charged.

Camurus will seek to engage pro-actively with the ODTP Post-market review to fully explore a Section 85 listing for Buvidal.