

# Clinical guidelines for use of depot buprenorphine (Buvidal<sup>®</sup> and Sublocade<sup>®</sup>) in the treatment of opioid dependence



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## Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and is based on the best available evidence at the time of development of this publication.

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## Acronyms

AE	Adverse Events
COWS	Clinical Opiate Withdrawal Scale
CS	Consensus Statement
DDIs	Drug Drug Interactions
Depot BPN	Depot Buprenorphine
FC	FluidCrystal®
IUGR	Intrauterine Growth Restriction
LAI BPN	Long Acting Injection Buprenorphine
LFT	Liver Function Test
MAOIs	Monoamine Oxidase Inhibitors
MATOD	Medication-Assisted Treatment of Opioid Dependence
NAS	Neonatal Abstinence Syndrome
NOWS	Neonatal Opioid Withdrawal Syndrome
NTX	Naltrexone
OAT	Opioid Agonist Treatment
OD	Opioid Use Disorder
SC	Subcutaneous
SL BPN	Sublingual Buprenorphine
SL BPN NX	Sublingual Buprenorphine / Naloxone
TGA	Therapeutic Goods Administration

# Contents

<b>Acronyms .....</b>	<b>3</b>
<b>Background to guideline for depot BPN for the treatment opioid dependence .....</b>	<b>9</b>
<b>1. Introduction to opioid agonist treatment (OAT) with depot BPN medications.....</b>	<b>10</b>
a. Overview of treatment model of care.....	10
b. Evidence of efficacy of depot BPN in the treatment of opioid dependence.....	11
<b>2. Clinical pharmacology .....</b>	<b>12</b>
a. Formulations .....	12
i. Buvidal® formulations.....	12
ii. Sublocade® formulations .....	12
b. Overview of pharmacokinetic properties.....	12
i. Absorption and onset of effects.....	14
ii. Metabolism.....	14
iii. Elimination and duration of effects.....	14
iv. Withdrawal, cravings, opioid blockade.....	15
c. Side effects and safety issues .....	15
i. Adverse events .....	15
ii. Contraindications.....	15
d. Special Warnings.....	16
i. Risk of serious harm or death with intravenous administration.....	16
ii. Risk of respiratory and central nervous system (CNS) depression.....	16
iii. Precipitation of opioid withdrawal in patients dependent on full agonist opioids.....	16
iv. Managing risks from concomitant use of benzodiazepines or other CNS depressants.....	16
v. Hepatitis, hepatic events and liver disease .....	17
vi. Use in patients at risk of arrhythmia .....	17
vii. Other medical conditions .....	18
viii. Driving, operating machinery.....	18
ix. Contraception advice.....	18
x. Pregnancy, breastfeeding and neonatal opioid withdrawal syndrome.....	18
xi. Drug–drug interactions (DDIs).....	20
<b>3. Providing treatment with depot BPN.....</b>	<b>21</b>
a. Selecting treatment options .....	21
b. Assessment and treatment planning.....	22
c. Client and clinician factors in choosing depot BPN compared with other OAT options.....	22

<b>4. Guideline regarding dosing regimens with depot BPN</b> .....	<b>26</b>
a. Commencing depot BPN Treatment .....	26
i. Overview of approaches to initiating depot BPN.....	26
b. Transitioning from SL BPN treatment .....	26
i. Commencing treatment with Buvidal® .....	26
ii. Commencing treatment with Sublocade® .....	28
c. Key principles in titrating depot BPN doses - adjusting dose and frequency of doses (CS).....	30
d. Supplemental BPN dosing (CS).....	30
i. Supplemental dosing for patients treated with Buvidal® .....	31
ii. Supplemental sublingual dosing for patients treated with Sublocade® .....	31
e. Transfer between Buvidal® and Sublocade® (CS).....	31
i. Transfer from Sublocade® to Buvidal® .....	31
ii. Transfer from Buvidal® to Sublocade® .....	32
f. Induction from other opioids: prescription opioids and methadone.....	32
g. Administering depot BPN injections .....	32
i. Administering Buvidal® injections .....	32
ii. Administering Sublocade® injections.....	32
h. Specific issues of delivering OAT with depot BPN .....	32
i. Intoxicated presentations.....	32
ii. Transfer of care.....	33
i. Prescription charting.....	33
<b>5. Discontinuing depot BPN treatment</b> .....	<b>34</b>
a. Withdrawing off depot BPN (with goal of opioid abstinence).....	34
b. Transfers to SL BPN (CS) .....	35
i. For Sublocade® to SL BPN.....	35
ii. For Buvidal® to SL BPN .....	35
c. Transfer to methadone or other opioid analgesics (CS) .....	35
d. Transfer to oral naltrexone (CS) .....	36
<b>6. Clinical conditions</b> .....	<b>37</b>
a. Overdose .....	37
b. Polydrug use and regular intoxication .....	37
c. Acute pain management in patients in depot BPN treatment.....	37
d. Chronic pain management in patients in depot BPN treatment .....	38
e. Surgical removal of depot BPN .....	38
<b>7. Use of depot BPN for withdrawal treatment</b> .....	<b>39</b>

<b>8. Special populations and settings .....</b>	<b>40</b>
a. High risk or vulnerable populations .....	40
i. Aboriginal people .....	40
b. Hospital and correctional settings.....	40
i. Correctional settings.....	41
c. Residential rehabilitation and supported housing settings.....	41
<b>9. Managing travel .....</b>	<b>42</b>
a. Local travel.....	42
b. Interstate transfer.....	42
c. Overseas travel.....	42
<b>10. Patient information and perspective (NUAA).....</b>	<b>43</b>
<b>11. Governance issues .....</b>	<b>45</b>
a. Acquisition .....	45
b. Storage .....	45
i. Buvidal®.....	45
ii. Sublocade®.....	45
c. Accountability.....	45
d. Authority to prescribe and administer buprenorphine injections .....	46
<b>12. References.....</b>	<b>47</b>
<b>13. Appendix.....</b>	<b>49</b>
a. Drug drug interactions (DDIs).....	51
b. Depot BPN studies .....	53
c. Pregnancy statement – checklist .....	55
d. Buvidal® Weekly product information AUS.....	55
e. Buvidal® Monthly product information AUS .....	55
f. Sublocade® product information AUS .....	55
g. Sublocade® prescribing information US.....	55



**Table 1: Overview of buprenorphine products available for treatment of opioid dependence in Australia**

	SL Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Formulations	Suboxone® contains buprenorphine (BPN) and naloxone in 4:1 ratio 2/0.5mg and 8/2mg sublingual film Subutex® contains buprenorphine in 0.4mg, 2mg and 8mg sublingual tablets	Buvidal® Weekly and Monthly contain BPN in FluidCrystal® injection depot technology Subcutaneous (SC) injections in prefilled syringes with 23 gauge needle. Administration via upper arm, thigh, abdomen or buttocks Buvidal® Weekly: 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL; 32mg/0.64mL Buvidal® Monthly: 64mg/0.18 mL, 96mg/0.27 mL; 128/0.36 mL	Sublocade® contains BPN in the ATRIGEL® Delivery System SC injections in prefilled syringes with 19 gauge needle administered in abdomen Monthly doses: 100mg/0.5mL or 300mg/1.5mL
Storage requirements	Store at room temperature (below 30°C)	Store at room temperature (below 25°C) Do not refrigerate or freeze.	Cold storage requirements (2-8°C). May be stored at room temperature (below 25°C) for up to 7 days before use Remove from cold storage for at least 15 minutes prior to SC injection
Clinical pharmacology	Bioavailability 10-30% Onset effects within 1 hour, with peak effects 2-4 hours after dose Duration effects usually 24 hours but dose dependent and can vary from 8 to 72 hours	Bioavailability = 100% Time to peak plasma level ( $t_{max}$ ) • Buvidal® Weekly = 24hrs • Buvidal® Monthly = 6-10 hrs Half life • Buvidal® Weekly = 3-5 days • Buvidal® Monthly = 19-25 days Steady-state equilibrium by 4 <sup>th</sup> dose	Bioavailability = 100% Time to peak plasma levels ( $t_{max}$ ) = 24hrs Half life = 43 to 60 days Steady-state equilibrium by 2 <sup>nd</sup> (300/100mg) to 6 <sup>th</sup> dose (300/300mg)
Frequency of dosing	Daily, two or three day doses Take-aways and unsupervised dosing available for low risk	Buvidal® Weekly dose can be administered every 7±2 days (5-9 day schedule) Buvidal® Monthly dose can be administered every 4±1 weeks (3-5 week schedule)	Sublocade® dosed every 4 weeks (26-42 day schedule)
Key Drug - Drug Interactions (DDIs)	Systemic BPN DDI include: - Opioids agonists: can reduce effects other opioids (blockade); BPN may precipitate withdrawal on induction - Sedatives (e.g. benzodiazepines, alcohol, TCAs, antipsychotics, gabapentinoids): sedation, respiratory depression, overdose A number of potential DDI can occur but are rarely of clinical significance (e.g. interactions with medications that induce or inhibit CYP450 and can lower or increase BPN plasma levels); or are rare (e.g. serotonergic syndrome in combination with medication such as SSRIs, MAOIs, tramadol); or medications that can cause QT prolongation and increase the risk of cardiac arrhythmias). Long duration of effects of depot BPN products precludes timely dose adjustment for DDI. If concerned re: potential DDI - initiate treatment with 'short acting' SL BPN for 1-4 weeks, monitor DDI and adjust medications accordingly, prior to transfer to depot injection.		

	SL Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Recommended dosing regimen Commencing treatment	<p>From heroin, morphine:</p> <ul style="list-style-type: none"> <li>• Commence 8mg Day 1 when patient in early / mild opioid withdrawal (usually &gt;8-12hrs after last dose or use).</li> <li>• Titrate upwards on daily basis as required.</li> </ul> <p>From methadone:</p> <ul style="list-style-type: none"> <li>- Initiate BPN when patient in moderately severe withdrawal (e.g. COWS<sub>≥</sub>12) (e.g. 1-2 days after last methadone dose)</li> <li>- Day 1: 2mg + 6mg after 1-2 hrs, with additional 2-8mg doses every 2-4 hrs as required to alleviate opioid withdrawal.</li> <li>- Day 2 onwards: titrate BPN dose daily as required.</li> </ul>	<ul style="list-style-type: none"> <li>- Buvidal® dose should be determined according to patient's SL BPN dose (see Table 5 sublingual and depot Buvidal® Weekly and Buvidal® Monthly doses for conversions)</li> <li>- Titrate subsequent doses after clinical review.</li> <li>- Note increasing effects during first few doses (accumulation to steady state after about 4 doses)</li> </ul> <p>Buvidal® may be initiated directly (without transition via SL BPN) if required (see section 4b Initiating directly to Buvidal® (CS)). Initiate 24mg Buvidal® Weekly dose, and titrate dose until stable.</p>	<p>Initiate treatment with SL BPN (at least 8mg) for ≥7 days, then transfer to Sublocade®.</p> <p>Recommended induction:</p> <ul style="list-style-type: none"> <li>- 300mg monthly injections x 2 doses (8 weeks)</li> <li>- then 100mg monthly doses (if patient 'stable' on initial 2 x 300mg doses) or 300mg monthly doses if require additional BPN effects (e.g. cravings, withdrawal, continued opioid use)</li> </ul> <p>Patients may be initiated with 100mg Sublocade® (after at least 7 days SL BPN treatment) doses if</p> <ul style="list-style-type: none"> <li>- safety concerns (e.g. severe hepatic disease)</li> <li>- DDI concerns: e.g. overdose risk from polysubstance use</li> </ul> <p>There is no published safety data for initiating Sublocade® in patients on low dose SL BPN (&lt;8mg), and Buvidal® should be preferred for such patients.</p>
Maintenance phase	<p>Adjust dose to achieve treatment goals (reduced use of other opioids, reduced withdrawal and cravings; blockade effects). Range 2-32mg daily; most patients require 12-24mg daily</p>	<p>Titrate dose to achieve treatment goals. Adjust doses when transferring between weekly and monthly doses</p>	<p>Titrate dose to achieve treatment goals. 100mg or 300mg monthly injections.</p>
Withdrawal phase	<p>Gradually taper dose over several weeks-months (e.g. 2-4mg weekly reductions)</p>	<p>Gradually taper doses (reducing dose strengths every 1-2 injections). Peak withdrawal features may emerge 4-12 weeks after last Buvidal® Monthly dose, or 1-4 weeks after last Buvidal® Weekly dose (CS).</p>	<p>Reduce dose to 100mg monthly injections prior to stopping. Peak withdrawal features may emerge 4-24 weeks after last 300mg dose or 4-12 weeks after last 100mg dose (CS).</p>
Key adverse events	<p>Systemic BPN adverse events</p>	<p>Systemic BPN adverse events Local injection site</p> <ul style="list-style-type: none"> <li>- Redness, pain, tenderness, swelling in approximately 5-10% patients.</li> <li>- Usually mild and transient and resolves spontaneously</li> </ul>	

# Background to guideline for depot BPN for the treatment opioid dependence

This Clinical Guideline has been developed to inform decision-making by clinicians and clients prescribing and / or being treated with the following long-acting injected depot buprenorphine (depot BPN) preparations:

*Buvidal® Weekly and Monthly* (developed under the product name CAM2038 q1w and q4w and manufactured by Camurus AB, and also known as Brixadi in the United States (US)) was registered by the Therapeutic Goods Administration (TGA) in Australia in November 2018 for ‘maintenance treatment of opioid dependence within a framework of medical, social and psychological support’.

*Sublocade®* (developed under the product name RBP-6000 and manufactured by Indivior) was registered by the TGA in Australia in July 2019.

At the time of writing, Buvidal® and Sublocade® formulations are awaiting decisions regarding Pharmaceutical Benefits Scheme (PBS) listing.

This guideline has been developed for treatment using depot BPN in the following settings, and assumes that the clinicians are familiar and experienced in the use of sublingual buprenorphine products in the treatment of opioid dependence:

- Public opioid treatment services, operated by Local Health Districts and Networks (including Justice Health & Forensic Health)
- Private opioid treatment (methadone and buprenorphine) clinics
- Community settings with health professionals experienced in the use of buprenorphine where a member of the treatment team holds a permit to prescribe buprenorphine for patients for the treatment of opioid dependence.

This guideline is to be used in conjunction with the NSW Clinical Guidelines: Treatment of Opioid Dependence – 2018 (1) and the National Guidelines for Medication-Assisted Treatment of Opioid Dependence 2014 (2). The authors expect that future state and national guidelines will be revised to incorporate depot BPN preparations.

This guideline document has been informed by a synthesis of:

- Published evidence for Buvidal® Weekly, Buvidal® Monthly (CAM 2038) and Sublocade® (RBP-6000)
- Product information for Buvidal® Weekly and Monthly registered in Australia with the TGA and in the EU by the European Commission (3, 4) and, Sublocade® registered in Australia with the TGA and in the USA with the Food and Drug Administration (FDA)
- The European Medicines Agency Assessment report for Buvidal (5)
- FDA submission for Sublocade®
- Treatment conditions and regulatory frameworks for the use of buprenorphine in the medication assisted treatment of opioid dependence (MATOD) in NSW (1, 2);
- Clinical experience in using depot BPN products in Australian clinical trials ([Appendix Depot BPN Studies](#))
- Consensus expert opinion of clinicians and consumer representatives including guideline working group formed by the Ministry of Health (MoH) and clinicians / consumers involved in pre-registration clinical trials of these products.

This is the first clinical guideline document for depot BPN treatment beyond clinical trials to be published in Australia. This guideline aims to provide a framework for clinical decision making by clinicians and consumers in a range of service settings involved in the delivery of treatment with depot buprenorphine products.

As clinical experience with depot BPN preparations is at an early stage, this guideline includes recommendations by clinical experts where research evidence does not currently exist. Wherever guidance is provided that is not directly informed by research evidence, the document will highlight these sections as “Consensus Statement” (CS).

It is anticipated that Australian and international research will be published in the near future that may change guidance recommended in this document. The document will be reviewed in 12 months.

# 1.

## Introduction to opioid agonist treatment (OAT) with depot BPN medications

### a. Overview of treatment model of care

OAT (e.g. with methadone or buprenorphine) has been demonstrated to be a safe and effective treatment approach for addressing opioid dependence and provides the opportunity to engage patients with other health and psychosocial interventions. The key elements of safe and effective OAT are (a) safe and effective use of medicine; (b) regular clinical reviews and monitoring; (c) participation in psychosocial interventions; and (d) addressing medical, mental health and social comorbidities.

Australia has hitherto been restricted to medications designed to be administered once a day (or up to three day intervals for a small proportion of patients treated with sublingual (SL) BPN). The risks associated with methadone and buprenorphine (diversion to others, injecting medications, overdose risks with methadone) have resulted in a treatment model in Australia that is predicated on supervised dosing at a specialist clinic, community pharmacy or correctional health service during the early stages of treatment, with take-away doses becoming available according to a risk assessment and risk mitigation strategies (1). The reliance on daily dosing impacts greatly upon the cost and inconvenience of treatment for patients and service providers, and has been cited as a barrier to engagement and retention for some patients in treatment.

The introduction of depot BPN formulations into the Australian treatment system represents a significant development in this model of care. The availability of buprenorphine treatment with once-a-week and once-a-month depot injections is expected to be associated with several potential benefits:

- *Greater convenience for patients in that they will not have to attend dosing sites (pharmacies, clinics) on a frequent basis for supervised dosing.* In Australia, most patients in SL BPN treatment attend daily or several times a week for supervised dosing. This in particular raises difficulties in regional and rural settings, where patients often have to travel large distances to reach dosing sites. This will also benefit patients for whom regular attendance at pharmacies is difficult (e.g. due to mobility problems, work issues, carers), or where regular attendance at a community pharmacy complicates confidentiality and can be associated with stigma and discrimination (e.g. in a rural town with only one pharmacy)
- *Reduced treatment costs for patients and service providers.* The Australian treatment system predominately involves supervised dosing (with some 'take-away' doses) at community pharmacies for which most patients pay between \$40 to \$50 per week or at private specialist clinics (patients pay up to \$100 per week); or attend public specialist clinics where the cost of dosing is borne by the government. This cost is a significant burden for many patients - many of whom are on unemployment or disability benefits, and is often cited as a reason for treatment drop-out in Australia. In addition, frequent attendance for dosing at a clinic or pharmacy is often associated with transportation costs for the patient. In the public system, staffing resources are largely utilised in supervised dosing rather than case management or providing health-related and/or psychosocial interventions, and it is envisaged that treatment with depot formulations should 'free' staff to attend to more therapeutic interventions than dosing.

- *Less risk of diversion and non-medical use of the medication, enhancing community safety.* Despite a treatment system predicated on supervised dosing and the predominant use of the buprenorphine-naloxone combination formulation, a significant minority of patients engage in non-medical use of buprenorphine (injecting, diversion to others, stockpiling) (6). This is of particular concern in some settings such as correctional settings, and has limited the use of buprenorphine in those settings across Australia
- *Greater medication adherence and enhanced treatment outcomes for some patients who struggle to attend regularly for dosing with SL BPN.* Some patients with opioid dependence struggle to attend regularly for dosing with SL BPN – either due to homelessness, cognitive impairment, domestic violence issues, child-care responsibilities, psychiatric co-morbidity, physical mobility problems (particularly with our ageing treatment population), or regular episodes of incarceration (e.g. police lock-up). Often these patients are also not suitable for large numbers of take-away doses of buprenorphine, and they often therefore find themselves in a cycle of missed doses, polydrug use, and deteriorating health and social conditions. Such patients may benefit from less frequent (e.g. weekly or monthly) dosing requirements with the depot product, yet maintain buprenorphine adherence and experience greater ‘stability’.

The introduction of depot BPN formulations is likely to have significant benefits for some patients and their service providers. However, it may not suit all patients in OAT, and some patients will prefer SL BPN or methadone treatment, and these options should be available. It is essential that patients are provided accurate information and options regarding their treatment, as part of informed decision making and consent.

## **b. Evidence of efficacy of depot BPN in the treatment of opioid dependence**

The efficacy and safety of Buvidal® and Sublocade® in the treatment of opioid dependence have been established in clinical trials. Flexible doses of weekly and monthly Buvidal® formulations were shown to be ‘non-inferior’ to SL BPN in a double blind RCT (7) on the primary endpoint of unsanctioned opioid use. Similarly, an RCT of Sublocade® (300/100mg and 300/300mg groups) demonstrated better treatment retention and significantly less unsanctioned opioid use than the placebo group (8), with no apparent differences between the two Sublocade® dosing regimens (300-100mg compared to 300-300mg dose conditions). There are no controlled studies comparing Sublocade® to ‘active’ buprenorphine or other forms of opioid agonist treatment.

See [Depot BPN Studies](#) for details of studies.

## 2.

# Clinical pharmacology

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. As a partial mu-opioid agonist, the effects of buprenorphine individuals are dose-dependent within a limited range, above which increasing dosages do not produce corresponding increases in effect. Thus, for certain pharmacologic effects (e.g., respiratory depression and sedation), buprenorphine may exhibit an enhanced safety profile compared with mu-opioid receptor full agonists. The clinical relevance of buprenorphine activity at kappa-opioid receptors remains unclear. Whilst extended-release buprenorphine formulations (e.g. 'low-dose' 7-day transdermal buprenorphine patches) have been available for the treatment of pain, the depot BPN formulations Buvidal® Weekly, Buvidal® Monthly and Sublocade® are a new generation of extended release 'medium-high dose' BPN formulations for the treatment of opioid dependence (9).

### a. Formulations

#### i. Buvidal® formulations

Buvidal® is a modified release formulation of BPN designed for administration by subcutaneous (SC) injection once a week (Buvidal® Weekly) or once a month (Buvidal® Monthly).

- Buvidal® Weekly is available in four dose strengths in prefilled syringes with a 23-gauge needle:  
8mg/0.16 mL, 16mg/0.32 mL, 24mg/0.48 mL or 32mg/0.64 mL BPN as the active ingredient.
- Buvidal® Monthly is available in three dose strengths in prefilled syringes with a 23-gauge needle: 64mg/0.18 mL, 96mg/0.27 mL or 128mg/0.36 mL BPN as the active ingredient.

Buvidal® depots contain the active substance BPN in delivery system compositions based on the proprietary FluidCrystal® injection depot technology – a lipid-based liquid. When injected into the SC tissue the FluidCrystal® formulation absorbs interstitial aqueous body fluid and transforms from liquid to highly viscous liquid crystal (or gel-like) phases *in situ*, which effectively

encapsulate the active substance. This results in a slow and consistent release of BPN, which can be controlled for a week or a month depending on the composition. Excipients are described in the Product Label (see Appendix)

#### ii. Sublocade® formulations

Sublocade® is an extended-release formulation of BPN, administered monthly by SC injection and provides sustained plasma levels of BPN over the monthly dosing interval. Sublocade® utilises the ATRIGEL® Delivery System. Sublocade® is injected as a liquid, and subsequent precipitation of the polymer creates a solid depot containing the BPN. After initial formation of the depot, BPN is released via diffusion from, and the biodegradation of, the depot.

Sublocade® is available in two dose strengths: 100mg/0.5 mL and 300mg/1.5 mL provided in a prefilled syringe with a 19 Gauge 5/8-inch needle.

### b. Overview of pharmacokinetic properties

The key pharmacokinetic properties of Buvidal® and Sublocade® are detailed in the Product Labels (see Appendices), and summarized in this section for comparison between the two products.

It is important to recognise that repeated use of the depot BPN formulations results in accumulation over time, and steady state equilibrium is achieved after approximately three to six weekly/monthly doses. The average ( $C_{avg}$ ), peak ( $C_{max}$ ) and trough ( $C_{min}$ ) BPN plasma concentrations seen at steady state (after four doses) of the various depot and SL BPN formulations are shown in [Figure 1 Pharmacokinetic parameters – steady state](#) – allowing a framework for comparing dose effects across different formulations.

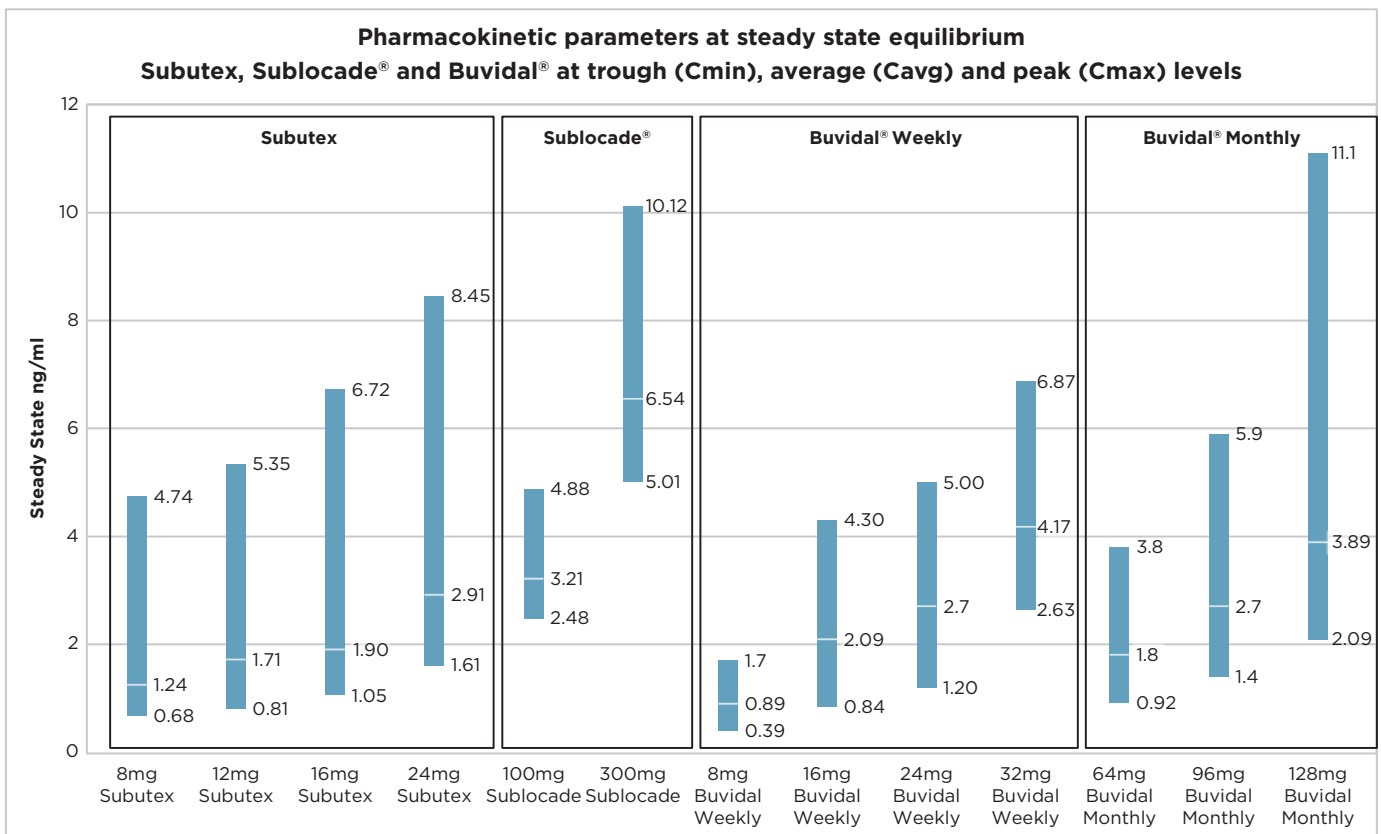
Whilst dose-proportional increases are seen within each category (sublingual, weekly and monthly) of BPN products, there is nevertheless considerable variation in BPN plasma levels between individuals, and these should be interpreted as guides only.

Brain imaging studies suggest that the suppression of signs and symptoms of withdrawal may require  $\geq 50\%$   $\mu$  opioid receptor occupancy ( $\mu$ ORO), which is often associated with BPN plasma concentrations  $\geq 1$  ng/mL; whereas opioid blockade (defined as the inhibition of the positive subjective effects (i.e., drug liking) of exogenous opioids) appears to require higher proportion (e.g.  $\geq 70$ -80%)  $\mu$ ORO, which is commonly associated with higher BPN plasma concentrations (e.g.  $\geq 2$ -3 ng/mL (10, 11)). These plasma levels are generally achieved by all depot BPN formulations.

Whilst laboratory receptor-binding studies are of interest in our understanding of this treatment approach, they do not translate into clinical practice readily, and there is no clinical role for monitoring buprenorphine plasma levels as part

of patient care. At this time, there is an inability to routinely or meaningfully measure BPN plasma levels or to assess opioid receptor occupancy in clinical practice: few laboratories have the capacity to accurately quantify buprenorphine and nor-buprenorphine levels, tests are not reimbursed by Medicare, requiring the patient or clinician to pay for the tests, and findings are very difficult to interpret – clinicians should focus more upon individual patient responses to treatment, with reviews of patient experience of withdrawal, cravings and continued substance use. Furthermore, continued heroin or other opioid use may be a result of inadequate BPN dose – but may also be related to social or other health issues, and dose is not the only factor to be considered.

**Figure 1: Pharmacokinetic parameters – steady state**



However, it should be emphasised that plasma BPN levels only partially account for the clinical (pharmacodynamic) effects experienced by patients – such as prevention of opioid withdrawal and cravings, and blockade effects. A range of other factors impact upon the clinical effects of BPN and must be considered when titrating BPN doses to achieve desired clinical outcomes – including patient expectancy, concomitant medical (e.g., chronic pain, hepatic disease) and

psychiatric conditions, use of other opioids and substances, drug-drug interactions and adverse events and genetic variation. Whilst expected plasma concentrations routinely achieved with formulations can serve as a guide to the selection of BPN doses and formulation, regular clinical patient monitoring is required. As previously highlighted, therapeutic monitoring of BPN plasma levels in clinical practice is not recommended at this time.

## i. Absorption and onset of effects

After SC injection, BPN peak concentrations are observed approximately 6-10 hours after the

Buvidal® Monthly injection, and approximately 24 hours after the Buvidal® Weekly and Sublocade® injections. After the initial BPN peak, the plasma BPN concentrations decrease slowly to a plateau.

Figure 2: Buvidal® Weekly and Buvidal® Monthly versus daily SL BPN

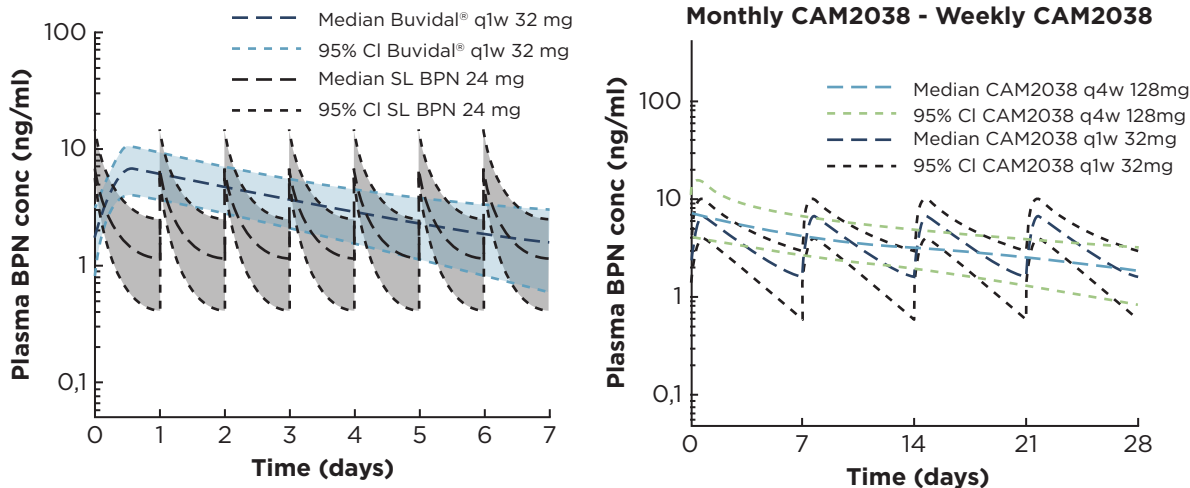
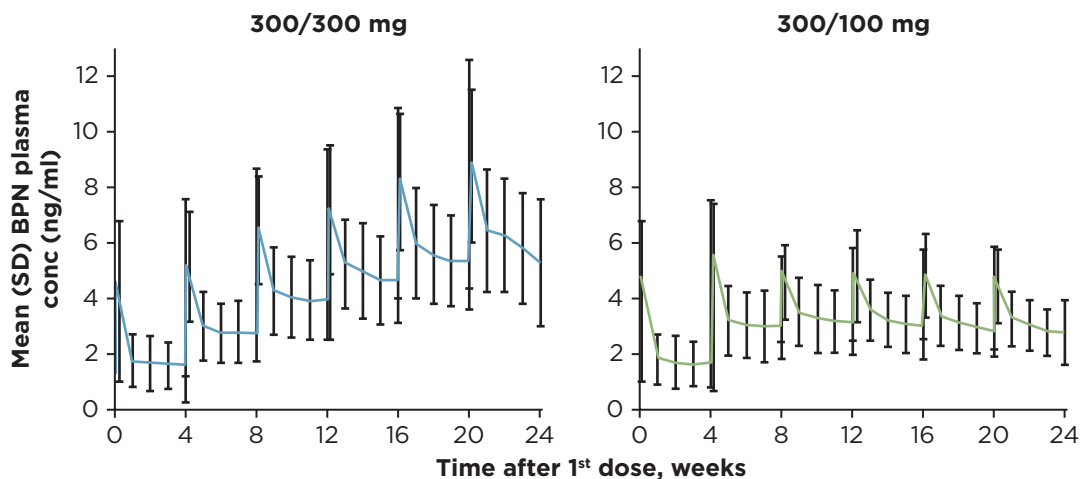


Figure 3: Sublocade® PK profile



## ii. Metabolism

The metabolism of BPN is largely the same irrespective of formulation. Variation in plasma terminal half-life and duration of effect is related to differences in the rate of release of BPN from the depot from the three different formulations. BPN is predominantly metabolised (N-dealkylation) by cytochrome P450 (CYP3A4) to the active metabolite norbuprenorphine, and both parent molecule and metabolite then undergo glucuronidation. Subcutaneous administration of depot BPN results in significantly lower plasma concentrations of norbuprenorphine metabolite compared to SL BPN, due to avoidance of first-pass metabolism invariably seen with some oral swallowing of sublingual doses.

## iii. Elimination and duration of effects

The slow release of BPN from the depot formulations results in extended duration of action of these products. The terminal plasma half-life of single doses of the depot formulations are:

- Buvidal® Weekly: 3 to 5 days
- Buvidal® Monthly: 19 to 25 days
- Sublocade®: 43 to 60 days

With repeated dosing, BPN plasma levels accumulate until steady state equilibrium is achieved typically by the five half-lives of dosing, and needs to be considered when adjusting doses during the first few weeks or months of treatment. For Buvidal® this typically means after the fourth dose (one month for Buvidal® Weekly, 4 months



for Buvidal® Monthly). For Sublocade® this means after the 6<sup>th</sup> month of the 300/300 regimen and however steady state is reached in the second month of the 300/100 mg regimen due to the loading effect of the first two 300 mg doses. The clinical effects of discontinuing depot BPN dosing will depend upon the formulation administered (weekly or monthly), the dose of depot administered (longer duration with higher doses), and the duration of treatment (whether steady state has been achieved following multiple doses).

Model simulations and clinical experience indicate that steady-state BPN plasma concentrations decrease slowly over time following the last injection and remain at therapeutic levels for extended periods – potentially up to 12 weeks (Buvidal® Monthly, Sublocade® 100mg) or up to 20 weeks (Sublocade® 300mg). The prolonged duration of effects of depot formulations may impact upon the (delayed) emergence of withdrawal symptoms, experience of adverse events, drug-drug interactions, and transitioning onto other opioid medications (e.g. SL BPN, methadone). It may also result in delayed ‘reduction’ of tolerance to opioids and be protective against overdose following resumption of heroin or other opioid use.

#### iv. Withdrawal, cravings, opioid blockade

Clinical trials indicate that both Buvidal® (7) and Sublocade® (8) are effective in reducing opioid withdrawal and cravings for opioid use. Withdrawal from stopping Buvidal® or Sublocade® are described in Section Depot BPN studies

‘Opioid blockade’ is defined as the inhibition of the positive physiological and subjective effects (i.e. drug liking) of exogenous opioids, and is achieved by BPN by its greater affinity for mu opioid receptors than conventional opioids such as morphine, heroin, methadone, oxycodone. The blockade of subjective opioid effects has been demonstrated with laboratory hydromorphone challenge studies with Buvidal® Weekly and Sublocade® products. These studies are summarised in the Appendix *Depot BPN Studies*

## c. Side effects and safety issues

### i. Adverse events

Side effects of depot BPN are similar to the known safety profile of BPN administered sublingually (2) (1), with the exception of adverse events related to injection of the drug (12). Readers are referred to product labels (see Appendices) for detailed information.

Table 2: Depot BPN Adverse Events

	Buvidal® PI	Sublocade® PI
<b>Injection site related adverse events</b>		
Pain	8.9%	7.2%
Pruritus	6.1%	6.6%
Induration	2.3%	1.4%
Bruising	0.5%	0.7%
Cellulitis	0.5%	0.4%
Swelling	4.2%	0.7%
Erythema	5.6%	4.7%
<b>Systemic adverse events</b>		
Nausea	7.0%	8.0%
Vomiting	4.2%	5.5%
Headache	7.7%	8.5%
Constipation	7.5%	8.0%

NB: this is not a head to head study – data has been taken from studies with different reporting frameworks (see PIs in Appendix for details)

### ii. Contraindications

Buvidal® Weekly or Buvidal® Monthly should not be administered to anyone hypersensitive to BPN (see below) or any of the excipients [phosphatidyl choline [soybean], glyceryl dioleate and ethanol anhydrous (in Buvidal® Weekly), and N-methyl-2-pyrrolidone (in Buvidal® Monthly)].

Sublocade® should not be administered to patients who have been shown to be hypersensitive (see below) to BPN or any component of the ATRIGEL® delivery system.

The features of hypersensitivity to BPN include rashes, hives, and pruritis. Most serious reported cases have involved bronchospasm, angioneurotic oedema, and anaphylactic shock. *It should be noted that hypersensitivity to buprenorphine is very rare.*

## d. Special Warnings

### i. Risk of serious harm or death with intravenous administration

Care must be taken to avoid inadvertent injection of depot BPN into a blood vessel or intradermally (into the skin). Intradermal injection may result in severe inflammation and local infection.

Intravenous injection presents significant risk of serious harm or death as depot BPN forms a depot upon contact with body fluids. Animal studies suggest that occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, may occur if administered intravenously.

### ii. Risk of respiratory and central nervous system (CNS) depression

BPN has been associated with life-threatening respiratory depression. Use depot BPN with caution in patients with significantly compromised respiratory function (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Due to its extended-release, if depot BPN is discontinued as a result of compromised respiratory function, monitor patients for ongoing BPN effects for several months.

### iii. Precipitation of opioid withdrawal in patients dependent on full agonist opioids

BPN may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists such as heroin, morphine, or methadone, if the first dose of BPN is initiated before the effects of the full opioid agonist have subsided (1, 2). Initiation of BPN treatment with SL BPN for period of 7-days or more removes risks of precipitated withdrawal on initiating depot BPN especially for patients on long acting opioids e.g. methadone. Verify that patients have tolerated and are stabilised on daily SL BPN for at least 7-days before commencing treatment with depot BPN.

If initiating depot BPN (Buvidal® only) directly from opioids other than SL BPN (See Section [Initiating directly to Buvidal® \(CS\)](#)) – there is a potential risk of precipitated withdrawal following the first dose of depot BPN if the patient is not in opioid withdrawal at time of first dose, and/or the

patient has not disclosed recent use of long acting opioids such as methadone. Whilst the slow onset of effects of the depot injections (Tmax 6-10 hours for Buvidal® Monthly; 24 hrs for Buvidal® Weekly, Sublocade®) suggests that precipitated withdrawal is unlikely to occur when initiating depot treatment, caution should be always exercised, with the first depot injection delayed until the patient is experiencing features of opioid withdrawal (e.g. a Clinical Opioid Withdrawal Scales (COWS) score  $\geq 12$ ) (2) Section A4). A 'test dose' of SL BPN (e.g. 4 or 8mg) may be warranted to exclude precipitated withdrawal if there are any clinical concerns, with commencement of depot BPN 2 or more hours later after the risk of precipitated withdrawal has been negated.

### iv. Managing risks from concomitant use of benzodiazepines or other CNS depressants

Depot BPN provides higher average blood levels over a weekly or monthly period compared to the daily changes in BPN blood levels with SL BPN (see *Overview of pharmacokinetic properties*). Concomitant use of BPN with Central Nervous System (CNS) sedatives (e.g. alcohol, benzodiazepines, TCAs, gabapentinoids and antipsychotic medications), increases the risk of adverse reactions, including overdose, respiratory depression, and death. It remains unclear whether these risks are increased or reduced with depot BPN compared with SL BPN treatments.

Options include the stabilisation, reduction or cessation of benzodiazepines or other CNS depressants (usually through a monitored and gradual taper (2), or decreasing the doses of other sedative medications to the lowest effective dose. Alternative medications and non-pharmacologic treatments for anxiety or insomnia should be considered. Ensure that other healthcare providers are aware of the patient's BPN treatment.

Consumer education regarding the risks of polysubstance use (including use of prescribed sedating medication), cautions regarding driving or operating machinery under such conditions, and the provision of take home naloxone interventions are important risk mitigation approaches.

## v. Hepatitis, hepatic events and liver disease

Moderate or severe hepatic impairment (Child Pugh B or C) slows down hepatic metabolism of BPN, resulting in higher plasma levels (estimated at 1.6 greater in Child B, 2.8 times greater Childs C) (13) and longer half-lives. Furthermore, cases of cytolytic hepatitis and hepatitis with jaundice have been (rarely) observed in individuals using BPN. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, other causes of pre-existing liver disease (e.g. viral hepatitis, use of other potentially hepatotoxic drugs such as alcohol) may have played a causative or contributory role. Acute hepatitis has been reversed on BPN cessation in some cases, but not others.

The effect of hepatic impairment on the pharmacokinetics of depot BPN has not been studied. Due to the long-acting nature of the product, adjustments to depot BPN dosages are not rapidly reflected in plasma BPN levels. Because BPN levels cannot be rapidly decreased, patients with *pre-existing moderate to severe hepatic impairment* (e.g. Child-Pugh B or C) are *not candidates for treatment with depot BPN*.

An assessment of hepatic function (including clinical examination and liver function tests) prior to treatment initiation with depot BPN is recommended if there are any concerns regarding pre-existing liver disease (e.g. viral hepatitis, alcohol use disorder). Where a patient is identified as having clinically relevant liver disease (more than a mild elevation of LFTs), then an extended period of treatment with SL BPN (e.g. one to three months) allows for monitoring of liver function to ensure that BPN does not worsen hepatic function, and for titration of BPN dose, prior to initiating depot BPN treatment.

Lower initial dose depot BPN dosing schedule (e.g. Buvidal® 8mg – 16mg weekly, 64mg monthly or Sublocade® 100mg monthly injections) should be considered for patients with significant hepatic impairment. Regular monitoring of liver function should occur for patients with persistent and severe liver disease whilst being treated with depot BPN (e.g. clinical examination, liver function tests 2 to 4 weeks early in treatment, and at 3-6 month intervals once stabilised), and underlying

causes (e.g. viral hepatitis, alcohol use) should be examined. Patients who develop moderate to severe hepatic impairment while being treated with depot BPN should be monitored regularly for several months for signs and symptoms of toxicity or overdose that may be caused by increased BPN plasma levels. Sedation following the initial dose may occur with high doses (e.g. Sublocade® 300mg), and patient should be warned accordingly. Termination of depot BPN treatment may be warranted if a patient's hepatic function significantly deteriorates, and specialist consultation is recommended. In one case, surgical removal of the Sublocade® depot was followed by improvement in liver enzymes (See appendix [Sublocade® prescribing information US](#)).

## vi. Use in patients at risk of arrhythmia

BPN has been observed to be associated with a prolonged QTc interval in some patients. Whilst in general, BPN should be avoided in patients with a history of long QT syndrome, or those taking Class IA antiarrhythmic medications (e.g. quinidine, procainamide, disopyramide), Class III antiarrhythmic medications (e.g. sotalol, amiodarone, dofetilide) or other medications that prolong the QT interval, existing evidence suggests that QTc prolongation and risk of arrhythmias appears to be greater with methadone, and commonly linked with other substance use, including alcohol, cocaine, and amphetamines. A risk-benefit decision should be made regarding opioid treatment for patients at risk of QT prolongation.

Key differences with depot BPN are that serum levels of BPN may be consistently higher than with SL BPN (see [Overview of pharmacokinetic properties](#)). For patients at risk, more intensive workup prior to and or monitoring whilst on depot BPN treatment may be required. For assessment and management see section 2.4.8 OAT Safety Issues – QT prolongation in the NSW Clinical Guidelines: Treatment of Opioid Dependence (1).

If there are significant concerns regarding BPN effects on QT prolongation, consider initiating and maintain treatment with SL BPN or weekly depot BPN treatment until all investigations (e.g. blood tests, ECG, 24hr-Holter) have been completed, as it is simpler to discontinue BPN using daily or weekly formulations.

## vii. Other medical conditions

Significant medical conditions that warrant caution with the use of depot BPN include:

- Orthostatic hypotension
- Elevation of cerebrospinal fluid pressure
- Cholestasis
- Acute abdominal conditions
- Adrenal insufficiency
- Poor respiratory function

For details see the product information for Buvidal® and Sublocade® ([Appendix Buvidal® Weekly product information AUS](#), [Buvidal® Monthly product information AUS](#), [Sublocade® product information AUS](#)). Assessment and management of patients with these conditions may require additional monitoring, consideration of the underlying aetiology and management plans. Where BPN treatment is required in patients with acute medical conditions such as those listed above, it may be prudent to use sublingual BPN treatment until the impact of BPN has been assessed, enabling easier dose titration and avoiding prolonged plasma levels from depot injections (that cannot be reversed)

## viii. Driving, operating machinery

BPN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. BPN plasma levels accumulate during the first four doses of Buvidal® and two (300/100mg) and six (300/300mg) doses with Sublocade®. Patients should be cautioned about driving or operating hazardous machinery until the prescriber and patient are satisfied that depot BPN does not adversely affect their ability to engage in such activities. People on a stable dose may not be at higher risk, providing the dose has been stabilised over some months and they are not using other impairing drugs.

Jurisdictional regulations on fitness to drive should also be considered.

A procedural outline “The Managing Driving Safety Awareness for At Risk Clients” template is available at: <https://www.health.nsw.gov.au/aod/professionals/Pages/driver-safety-example-template.aspx>

## ix. Contraception advice

Women on buprenorphine should be provided with advice regarding contraception as part of routine care when commencing opioid treatment and on an ongoing basis during treatment (Sec A.4.2 and A.7).

## x. Pregnancy, breastfeeding and neonatal opioid withdrawal syndrome

BPN is a first line treatment (alongside methadone) for the treatment of opioid dependence in pregnancy (1, 14-16). BPN and methadone treatment, provided with adequate antenatal care, are associated with reduced maternal heroin use, reduced fetal death, increased neonatal birth weight and decreased premature delivery (14, 16). In 2018, the TGA product listing of SL BPN (both Subutex and Suboxone) changed so that pregnant and breastfeeding are no longer contraindications in Australia (17, 18) and are listed as Category C medications in pregnancy (as is methadone).

There is a lack of research data on the safety and effectiveness of depot BPN formulations in pregnancy and breastfeeding. While BPN is the principal component of depot BPN, two principal differences exist compared to SL BPN:

- Higher and more stable maternal blood levels of BPN than typically seen with sublingual BPN treatment
- Excipients in Buvidal® Weekly, Buvidal® Monthly and Sublocade®.

The individual risk and benefits of continuing any medication, and other medication options should be considered during pregnancy. Pregnant women on depot BPN may be transferred to SL BPN. However, there may be clinical situations where pregnant women may not easily transfer to SL BPN (e.g. lack of access to daily sublingual treatment dosing) or it may be considered that a pregnant woman is more likely to remain stable on depot BPN rather than transferring to sublingual treatment (i.e. the risks of transfer to sublingual treatment may outweigh the expected benefits).

Depot BPN should be used during pregnancy only if the potential benefit justifies the potential risks to the mother and baby. Refer appendix [Pregnancy Statement – Checklist](#) for a checklist to continue on depot BPN during pregnancy.

N methyl 2 pyrrolidone (NMP) is an excipient in Buvidal® Monthly and Sublocade®. Buvidal® Weekly does not contain NMP.

NMP is listed under the Australian Standard For The Uniform Scheduling Of Medicines And Poisons (19) under schedule 5: Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label. However, the levels of NMP in both Buvidal® Monthly and Sublocade® are less than the threshold for listing in this schedule (i.e. less than 25% of the product).

Whilst the mutagenic potential of NMP is weak, there is preclinical evidence of toxicity of NMP on rats and other animals, including decrease in fetal weight. A dose response effect is preclinical studies is noted, with adverse effects not being reported at lower NMP levels. In animals models the no observed adverse effect level was 160 to 237 mg/kg body weight, depending on route and species (20).

There is a lack of human data on exposure to NMP during pregnancy. There is a single case report of NMP exposure during pregnancy in a laboratory technician. The technician had repeated daily inhalation exposure to NMP from early pregnancy with direct dermal contact through a solvent spill at week 16. At week 20 IUGR was noted. At week 31 the technician delivered a stillborn baby. It is not possible to establish a causal relationship of NMP exposure during pregnancy and the stillbirth in this case (21-23).

#### **a) Buvidal®**

Pregnancy and breastfeeding are listed as a contraindications to Buvidal® Weekly and Buvidal® Monthly in the Australian product information (3, 4).

Buvidal® Weekly contains BPN and soy phosphatidyl choline [soybean], glyceryl dioleate and anhydrous alcohol. Soybean phosphatidylcholine is a refined lipid product but can contain traces of soya protein. Hypersensitivity to soybean produced products is a known, but very rare, adverse event in the general population (24). There are no current concerns regarding exposure to glyceryl dioleate or soy phosphatidyl choline during pregnancy, indeed phosphadityl has been suggested as a supplement during pregnancy (25). The maximum level of ethanol in Buvidal® (weekly product, 32mg) is less than 100mg (note on standard

alcohol drink =10g of ethanol). According to EU regulations <100mg ethanol is not considered a concern for 'pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy' (ref - EMA/CHMP/302620/2017 (25)).

Buvidal® Monthly contains BPN and soy phosphatidyl choline [soybean], glyceryl dioleate and N-methyl-2-pyrrolidone (NMP). For the amounts of NMP in Buvidal® Monthly see Table 3 List of Depot BPN excipients below.

Buvidal® Weekly and Buvidal® Monthly have been approved for use in pregnancy by the European Commission where benefits outweigh the risks. Pregnancy and breastfeeding are not listed as contraindications in the Buvidal® European product information.

#### **b) Sublocade®**

Sublocade® contains BPN and N-methyl-2-pyrrolidone (NMP) and Poly (DL-lactide-co-glycolide) (PLGA/polyglactin). PLGA is a biodegradable polymer with minimal associated toxicity and is approved by the FDA and EMA in drug delivery systems in humans (27). There are no current concerns regards PLGA exposure during pregnancy in preclinical models (28, 29). For the amounts of NMP in Sublocade® see Table 3 List of Depot BPN excipients below. Pregnancy and breastfeeding are not listed as contraindications in the Australian Sublocade® product information or USA Sublocade® prescribing information. (See appendix Sublocade® product information AUS (30)). The SAMSHA TIP 63 recommends "*Women should be advised that the use of Sublocade® during pregnancy should be considered only if the benefits outweigh the risks*" (31).

#### **c) Neonatal withdrawal**

Neonatal opiate withdrawal syndrome - NOWS (also known as neonatal abstinence syndrome (NAS) is an expected and, potentially life-threatening outcome (if not screened for, or treated) of prolonged opioid exposure during pregnancy. Advise pregnant women receiving opioid treatment with depot BPN of the risk of NOWS and ensure that appropriate treatment will be available as the onset and duration of NOWS may be longer (e.g. 24 to 48 hours after expected onset with SL BPN).

**Table 3: List of Depot BPN excipients**

Excipient	Buvidal® Weekly	Buvidal® Monthly	Sublocade®
soy phosphatidyl choline [soybean]	Yes	Yes	
glyceryl dioleate	Yes	Yes	
anhydrous alcohol	<100mg		
N-Methylpyrrolidone		57-114mg	278-833mg
Poly(DL-lactide-co-glycolide)			Yes

There are no data available to inform the onset, time course and severity of NOWS with depot BPN. While there is no further neonatal buprenorphine exposure following delivery, fetal buprenorphine exposure up until delivery may be higher than seen with SL BPN due to the different pharmacokinetic profile of depot BPN. Liaison with neonatologists/specialist paediatricians should occur regarding screening and treatment for NOWS for neonates exposed to depot buprenorphine during pregnancy.

Clinically it may be appropriate to monitor neonates for a longer period than seen with SL BPN exposure (e.g. 1-2 weeks).

#### d) Breastfeeding

Pregnancy and breastfeeding are listed as a contraindications to Buvidal® Weekly and Buvidal® Monthly in the Australian product information (3, 4). Serum level of BPN seen with depot treatment may be higher than seen with SL BPN treatment (refer section [Overview of pharmacokinetic properties](#)). However it is not anticipated that this will result in significantly higher BPN levels in breastmilk. While there is not a substantial literature regarding BPN exposure to infants due to breastfeeding (32) the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for depot BPN treatment and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

There may be clinical situations where breastfeeding women may not easily transfer to SL BPN (e.g. lack of access to daily sublingual treatment dosing) or it may be considered that a breastfeeding woman is more likely to remain stable on depot BPN rather than transferring to sublingual treatment (i.e. the risks of transfer to sublingual treatment may outweigh the expected benefits).

Depot BPN should be used during breastfeeding only if the potential benefits justifies the potential risks to the mother and baby.

Breastfeeding is not listed as a contraindication in the Buvidal® European product information, Australian Sublocade® product information or US Sublocade® prescribing information.

### xi. Drug-drug interactions (DDIs)

A number of potentially clinically relevant DDIs exist with BPN (1, 2), product information for both Buvidal® and Sublocade®) indicate:

- Interactions with other opioids (precipitated withdrawal, blockade effects)
- Interactions that increase the risk of overdose – as occurs with alcohol, other opioid drugs, benzodiazepines, tricyclic antidepressants, sedating antipsychotics and antihistamines) or through reductions in hepatic metabolism (Cytochrome P450 interactions) resulting in increased BPN plasma levels

Many of these DDIs are difficult to predict in advance, and generally require clinical monitoring and dose adjustment. However, the prolonged duration of effects of the depot BPN formulations makes sudden cessation of BPN and/or titration of BPN doses more difficult than when using SL BPN. If there are significant concerns regarding the clinical impact of DDIs, a period of treatment with SL BPN is recommended, enabling more refined dose adjustments.

A summary of the key drug-drug interactions, with recommendations regarding management, are described in Appendix [Drug drug Interactions \(DDIs\)](#).

# 3.

## Providing treatment with depot BPN

### a. Selecting treatment options

Opioid dependence is often associated with other harmful patterns of substance use (e.g. alcohol, amphetamines, benzodiazepines, cannabis, tobacco), and other medical, psychiatric and social problems. Addressing these issues involves coordinated treatment with other health and social service providers over an extended period.

OAT (e.g. with methadone or BPN) has been demonstrated to be a safe and effective treatment approach for addressing opioid dependence and provides the opportunity to engage patients with other health and psychosocial interventions. The key elements of OAT are:

- safe and effective use of medicine
- regular clinical reviews and monitoring
- participation in psychosocial interventions
- addressing medical, psychiatric and social comorbidities

Treatment with depot BPN formulations potentially challenges the way in which the components of OAT services are co-ordinated and structured. Conventional OAT with methadone and SL BPN treatment usually involves frequent attendance for (supervised) dosing, providing the opportunity to schedule regular clinical reviews, medical appointments and psychosocial interventions (e.g. counselling). For example, National Guidelines for Medication Assisted Treatment of Opioid Dependence (2) suggest regular and frequent (e.g. weekly) clinical reviews during the initial stages of treatment, during which medication doses and adverse events are reviewed, comprehensive assessments of comorbidities are completed, and therapeutic rapport between client and service providers is developed.

The less frequent dosing with depot BPN formulations may require a different approach to structuring clinical reviews, psychosocial interventions and treatment care planning.

One option may be to consider using the weekly depot BPN formulation (Buvidal® Weekly) when commencing treatment (e.g. for the first two to four weeks) until clinicians and patients become more familiar with depot BPN treatment and individual patient's treatment needs are clarified. It is also possible, however, to commence OAT with monthly BPN formulations (i.e. Buvidal® Monthly or Sublocade®). Even though the monthly BPN formulations are intended for 4 weekly injection intervals, clinicians may aim to schedule more frequent clinical reviews for patients initiating OAT or during periods of clinical instability, during which assessment, care planning activities and psychosocial interventions are scheduled. These issues should be discussed with individual clients when considering the choice of depot versus SL BPN treatment, and when developing treatment plans with clients. It should be emphasised that safe and effective OAT is more than the provision of medication, and that regular reviews, treatment planning, and psychosocial interventions are important elements of OAT.

Depot BPN treatment, (i.e. Buvidal® Weekly, Buvidal® Monthly and Sublocade®) is indicated for treatment of opioid dependence within a framework of medical, social and psychological support. In this context medical support may be provided by a medical practitioner (general practitioner, addiction medicine specialist, addiction psychiatrist or other medical practitioner) in conjunction with other clinical staff (e.g. nursing staff) providing depot medication injections. Social and psychological support may be provided by medical, nursing and/or other staff (including drug and alcohol workers, pharmacists, psychologists and other disciplines) depending on patient needs and resources available.

## b. Assessment and treatment planning

A comprehensive assessment is an essential component of safe and effective treatment, and aims to identify the pattern of substance use, key medical, psychiatric and social complications, and examine patient treatment goals and preferences. Assessment may take several appointments to complete the assessment. Details regarding assessing clients for OAT are described in national and local guidelines (1, 2).

Treatment planning needs to involve the patient, reflecting their preferences, circumstances and case complexity. It also often involves coordination across multiple health and welfare providers. A treatment care plan that addresses the patient's substance use, physical and mental health and social issues should be developed and documented for patients.

Informed consent is important in this area of health care. Patients should understand the implications of different treatment options, including potential risks and benefits, side effects, financial and other commitments. Patients should be provided with written information, and opportunities to ask questions regarding treatment options. Alternative communication methods may be required for patients with cognitive impairment, language and cultural factors.

## c. Client and clinician factors in choosing depot BPN compared with other OAT options

Research evidence and clinical experience supports the conclusion that both methadone and BPN are safe and effective in the treatment of opioid dependence. Key factors in choosing between methadone and BPN medications are described in National (S A.4.1) (2) and local guidelines, and include patient factors such as prior experience with medications, adverse events, DDIs, overdose risks, and in some cases logistic factors such as more flexible dosing options with BPN (alternate day dosing, unsupervised dosing) than methadone, which may in turn impact upon the inconvenience and cost of treatment for patients. Clinician factors may also play a part in choosing between methadone and BPN (e.g. accreditation of medical practitioner to prescribe one medication over another).

There is minimal research evidence to guide decisions regarding the choice between the depot BPN formulations (Buvidal® Weekly, Buvidal® Monthly and Sublocade®) and SL BPN treatment, and individual patient and clinician factors need to be considered (see There is minimal research evidence to guide decisions regarding the choice between the depot BPN formulations (Buvidal® Weekly, Buvidal® Monthly and Sublocade®) and SL BPN treatment, and individual patient and clinician factors need to be considered (see Table 4 Differences between SL and depot BPN (Buvidal® and Sublocade®)).



**Table 4 Differences between SL and depot BPN (Buvidal® and Sublocade®)**

	Sublingual formulations	Buvidal® (weekly and monthly depot BPN)	Sublocade® (monthly depot BPN)
Convenience of dosing	OAT dosing requirements are determined at local jurisdictional level. In principle, treatment with SL BPN formulations require supervised dosing at the onset of treatment, with increased access to take-away doses and unsupervised dosing according to a risk – benefit assessment. Alternate-day and three-day dosing are options for some patients – however are often ineffective in patients on high daily doses (e.g. 24mg or more).	Depot BPN dosing will greatly reduce the need for regular attendance at a pharmacy / clinic for doses. This may be particularly relevant for those who are unable to attend regularly for dosing (e.g. travel, work, childcare, mental health and homelessness)	
If on current low S/L BPN dose	Patients effectively treated with low daily SL BPN doses (<4mg) may be unwilling to increase their ‘BPN levels’ by transitioning to depot BPN – particularly monthly products.	The lowest Buvidal® Weekly dose (8mg) is broadly equivalent to 2-6mg SL BPN daily; whilst the lowest Buvidal® Monthly dose (64mg) is broadly equivalent to 8-10mg BPN SL daily. Patients effectively treated with low daily SL BPN doses (<4mg) may be unwilling to increase their BPN levels by transitioning to monthly depot doses, and consider use of Buvidal® Weekly for these patients.	100mg doses are equivalent to moderate (e.g. ≥8mg) SL BPN doses, with the 300mg dose equivalent to doses >16mg. Patients effectively treated with low daily SL BPN doses (<8mg) may not be keen to increase their BPN levels by transitioning to Sublocade®, and Buvidal® should be the preferred depot medication.
Previous exposure and experience with BPN	Patients with no prior BPN exposure should have a period of SL treatment that is sufficient to establish if there are any ongoing concerns with BPN treatment (adverse events, DDIs) warranting its discontinuation. This can generally be established rapidly with SL BPN (e.g. within seven days).	Patients with prior BPN treatment should have a good understanding of any likely adverse events or DDIs that will be relevant to them, and transition to depot BPN can be confidently made after the initial 7-days of SL treatment, or directly to Buvidal® products.	
Duration between doses	SL BPN lasts 24 hrs, second and third daily dosing available	There is evidence for inducting patients directly on to Buvidal® Weekly without initial SL BPN treatment, enabling direct initiation where SL BPN treatment is not preferred.	Sublocade® enables dosing every 26 to 42 days or longer. Individual variation will occur
		Buvidal® Weekly enables dosing every 5-9 days (and possibly up to 14 days for some patients). Buvidal® Monthly enables dosing every 3-5 weeks (and possibly up to 8 weeks for some patients). Individual variation will occur	

	Sublingual formulations	Buvidal® (weekly and monthly depot BPN)	Sublocade® (monthly depot BPN)
Side effects	In general, adverse events to BPN are similar for both SL and depot BPN, with the exception of injection related adverse events - which tend to be transient and mild in most cases.		
	It is easier to adjust the BPN dose and even discontinue dosing when using SL BPN.	If there are concerns regarding BPN related adverse events, particularly dose related adverse events (e.g. severe hepatic disease), patients should be initially treated and stabilised on SL BPN, allowing for assessment and management of adverse events before transitioning to depot BPN. Moderate or severe injection related adverse events that do not spontaneously resolve are a reason to discontinue depot BPN and transition to SL BPN treatment. Ensure good SC injection technique is occurring.	
Drug interactions	In general, BPN DDIs are similar for both SL and depot BPN formulations. The ease of dose adjustment with SL BPN treatment suggests it should be preferred if there are concerns regarding potential clinically significant DDIs.	If concerns regarding significant DDI – consider a period of treatment with SL BPN enabling easier dose titration (and discontinuation if required).	
Pregnancy and breastfeeding	Australian clinical guidelines support the use of SL BPN as a first line agent alongside methadone for opioid dependence in pregnancy and during breastfeeding. Neonates should be screened and treated for neonatal abstinence if this emerges. Paediatric follow up is recommended for children exposed to opioids and other drugs in utero.	Due to the lack of research data on the outcomes of pregnant women and their offspring during depot BPN treatment, transfer to SL BPN treatment should be considered. However, after a risk benefit discussion it may be appropriate for pregnant / breastfeeding women to continue weekly depot BPN treatment. The risk of destabilizing and relapse by switching to sublingual in a pregnant patient who had been progressing well on depot buprenorphine, and consequent risks of opioid and other drug use to the developing fetus, need to be considered.	
Unstable medical, psychiatric and social conditions	Patients with unstable clinical presentations often require frequent clinical reviews and interventions. Frequent attendance for SL BPN dosing can provide an opportunity to better engage some clients.	Consider Buvidal® Weekly for patients that require more frequent monitoring than can be achieved with monthly doses.	
Concomitant medication supply.	Adherence with concomitant medications can be enhanced through daily dosing or interval dispensing. This may be particularly relevant for patients taking medications that require high levels of adherence for effectiveness (e.g. antibiotics), or due to safety (e.g. other psychoactive medications)	Adherence may be linked to weekly attendance for patients on Buvidal® Weekly.	

	Sublingual formulations	Buprenorphine (weekly and monthly depot BPN)	Sublocade® (monthly depot BPN)
Cost of treatment	Frequent dosing increases costs for patient travel. Public treatment – costs are borne by the state, community pharmacy dosing, costs are borne by the patient – and usually \$35-45/week, private clinics more	Fewer transport costs for patients with less frequent attendance for dosing. Cost of depot BPN are yet to be determined.	Fewer transport costs for patients with less frequent attendance for dosing. Cost of depot BPN are yet to be determined.
Risks of non-medical medication use, for example diversion or injection	SL BPN formulations are associated with a risk of aberrant use (e.g. injecting BPN) and/or diversion (use by others) of SL BPN formulations – either of unsupervised doses, or doses ‘removed’ from a dosing site (e.g. pharmacy, clinic).	Consider using depot BPN where there are concerns regarding non-medical use (e.g. injecting, hoarding) or diversion of SL BPN (including custodial settings).	
Takeaway / unsupervised dosing	‘Take-aways’ and/or unsupervised dosing regimens are appropriate for patients assessed as low risk of poor medication adherence, and to enhance patient autonomy. Some patients do not meet eligibility for frequent take-away or unsupervised dosing.	Depot BPN may be preferred where a patient has a number of risk factors for take-aways or unsupervised dosing that are difficult to mitigate. This may include high risk substance use, or history of non-medical medication use (e.g. injection) or diversion.	
Goal of withdrawal from OAT	Withdrawal is associated with relapse to opioid use, increase in risk of opioid overdose immediately after ceasing OAT, overdose prevention strategies (e.g. take-home naloxone), after care advised.	Unclear regarding whether withdrawal from depot BPN results in better outcomes (severity and duration of withdrawal symptoms, relapse rates, deterioration health, patient experience) than withdrawal from SL formulations.	

# 4.

## Guideline regarding dosing regimens with depot BPN

### a. Commencing depot BPN Treatment

#### i. Overview of approaches to initiating depot BPN

Most patients commencing depot treatment in Australia will already be in long-term treatment with SL BPN.

For others initiating BPN treatment, a short period (e.g.  $\geq 7$ -days) of sublingual treatment with BPN (as Subutex or Suboxone) is generally recommended prior to transitioning to depot BPN treatment. This may be for three principal reasons:

- to ensure patients do not experience significant adverse events (e.g. headaches, nausea, sedation) or other concerns (e.g. DDI) when initiating BPN treatment
- to minimise risks of precipitated withdrawal when initiating BPN treatment, particularly for those with recent methadone treatment.
- to ensure the patient is satisfied with BPN treatment choice.

Local guidelines (1, 2) should be followed when initiating SL BPN in this situation (2). Longer periods of SL BPN treatment may be required prior to initiating depot BPN treatment if the patient reports BPN related adverse events or DDIs, has existing severe liver disease or is finding it difficult to stabilise on a dose of SL BPN.

However it should be noted that direct initiation of Buvidal<sup>®</sup> treatment from short acting opioids (e.g. heroin, morphine, oxycodone) without an intervening period on SL BPN can occur (see [Initiating directly to Buvidal<sup>®</sup> \(CS\)](#)).

Transfers from long acting opioids (methadone) should only occur via SL BPN, as there is little experience or research of initiating depot treatment directly from methadone.

### b. Transitioning from SL BPN treatment

#### i. Commencing treatment with Buvidal<sup>®</sup>

Patients treated with SL BPN or SL BPN NX may be transitioned directly to Buvidal<sup>®</sup> Weekly or Buvidal<sup>®</sup> Monthly starting on the day after the last daily SL treatment dose, see recommendations in Table 5 sublingual and depot Buvidal<sup>®</sup> Weekly and Buvidal<sup>®</sup> Monthly doses. Individual clinical titration of doses may be required on subsequent doses, recognising that the dose effects of the depots are likely to increase with BPN accumulation until steady state equilibrium is achieved (usually after 3 to 5 doses).

Patients can be transferred directly onto either weekly or monthly injections from sublingual BPN. Factors that may lead to the clinician and patient choosing weekly over monthly treatment may include: desire for more frequent clinical review or concomitant use of benzodiazepines, alcohol or other sedatives (See Table 5 sublingual and depot Buvidal<sup>®</sup> Weekly and Buvidal<sup>®</sup> Monthly doses).

**Table 5: Sublingual and depot Buvidal<sup>®</sup> Weekly and Buvidal<sup>®</sup> Monthly doses**

Daily SL BPN dose	Buvidal <sup>®</sup> Weekly depot dose	Buvidal <sup>®</sup> Monthly depot dose
$\leq 6$ mg	8mg	No monthly equivalent
8-10mg	16mg	64mg
12-16mg	24mg	96mg
18-32mg	32mg	128mg

#### **a) Initiating directly to Buvidal<sup>®</sup> (CS)**

Whilst the Therapeutics Goods Administration has recommended 7 or more days of treatment with SL BPN treatment prior to commencing depot Buvidal<sup>®</sup> treatment, there is considerable

international clinical experience and evidence (7, 12) regarding the safety and efficacy of direct initiation onto Buvidal® Weekly without a ‘run in’ period of SL BPN. As such, there is sufficient evidence to recommend that Buvidal® Weekly may be initiated directly from short acting opioids (e.g. heroin, morphine, oxycodone, fentanyl) without the need for SL BPN treatment. This may be particularly pertinent where:

- patient has previously experienced BPN treatment and confident that there is no hypersensitivity or other significant adverse events to BPN
- the patient has a preference for initiating depot treatment directly without SL dosing
- rural or regional settings, with limited dosing options (pharmacy) for sublingual dosing
- patients having to travel significant distances to attend pharmacies/clinics for sublingual dosing
- travel costs and dosing fees patients cannot afford

Clinical judgement should be used to assess the patient’s needs for long acting opioid treatment with the TGA recommendation to prescribe SL BPN prior to commencing Buvidal® Weekly. Patients should be informed that this is ‘off-label’ practice, and the rationale for direct induction and patient informed consent documented in clinical medical records. Patients should be reviewed regularly if inducting directly onto Buvidal® Weekly.

In situations where it is clinically appropriate to commence Buvidal® Weekly from heroin or other non-prescribed opioid use (e.g. non-medical use of oxycodone) the following starting doses are recommended: weekly 24 mg, with the option of an additional 8 mg ‘top up’ dose at least one day apart within the first week as required.

To avoid the risk of precipitated withdrawal, the first Buvidal® administration in patients not currently on SL BPN or SL BPN NX should be started when objective and clear signs of mild to moderate withdrawal are evident (e.g. COWS score of 10 or more) or after receiving at least one dose of SL BPN without precipitated withdrawal. A single sublingual ‘test’ dose of 4mg – 8mg BPN may be clinically appropriate in this situation (1).

### **b) Titrating doses of Buvidal® (CS)**

After selecting the appropriate weekly or monthly dose of Buvidal® (Table 5 sublingual and depot Buvidal® Weekly and Buvidal® Monthly doses), patients can usually continue on these doses without experiencing cravings, withdrawal symptoms or reporting significant heroin or other non-prescribed opioid use. Four doses are required to achieve steady-state plasma levels (see [Buvidal® Weekly product information AUS](#), [Buvidal® Monthly product information AUS](#)).

However, clinical titration of Buvidal® Weekly or Buvidal® Monthly may be required if patients present with significant opioid withdrawal during the first three to four doses of Buvidal®, whilst steady state plasma levels are being reached. Buvidal® should be administered weekly or monthly according to individual patient’s needs and clinical judgement and at doses established after initiation or switching. In previous research (12) approximately 10-20% of patients adjusted their Buvidal® dose (up or down) in the subsequent few doses following the initial Buvidal® dose.

The key principles in titrating buprenorphine doses are described in section [Key principles in titrating depot BPN doses – adjusting dose and frequency of doses \(CS\)](#) below.

### **c) Supplemental or ‘top-up’ BPN doses (CS)**

‘Top-up’ or supplemental doses of Buvidal® may be given if the patient experiences clinical features of opioid withdrawal, cravings or persistent unsanctioned opioid use (see [Supplemental BPN dosing \(CS\)](#)) If clinically indicated after the initial 24 hours after a Buvidal® dose, patients on Buvidal® may receive additional 8mg Buvidal® Weekly injections. Supplemental doses of Buvidal® 8mg weekly may be given during a dosing period, up to a maximum dose of 32mg for the weekly injections (Buvidal® Weekly) and 160mg for the monthly injections (Buvidal® Monthly). There must be at least one day between each supplemental 8mg injection.

There may be circumstances where top up or supplemental doses of BPN are required but Buvidal® Weekly 8mg doses are not possible to organise (e.g. travel away from regular service providers). Supplemental low doses of SL BPN (e.g. 4mg or 8mg) may be used for a limited period of time until the next depot injection can be organised.

**d) Buvidal® flexible dosing schedules and missed doses**

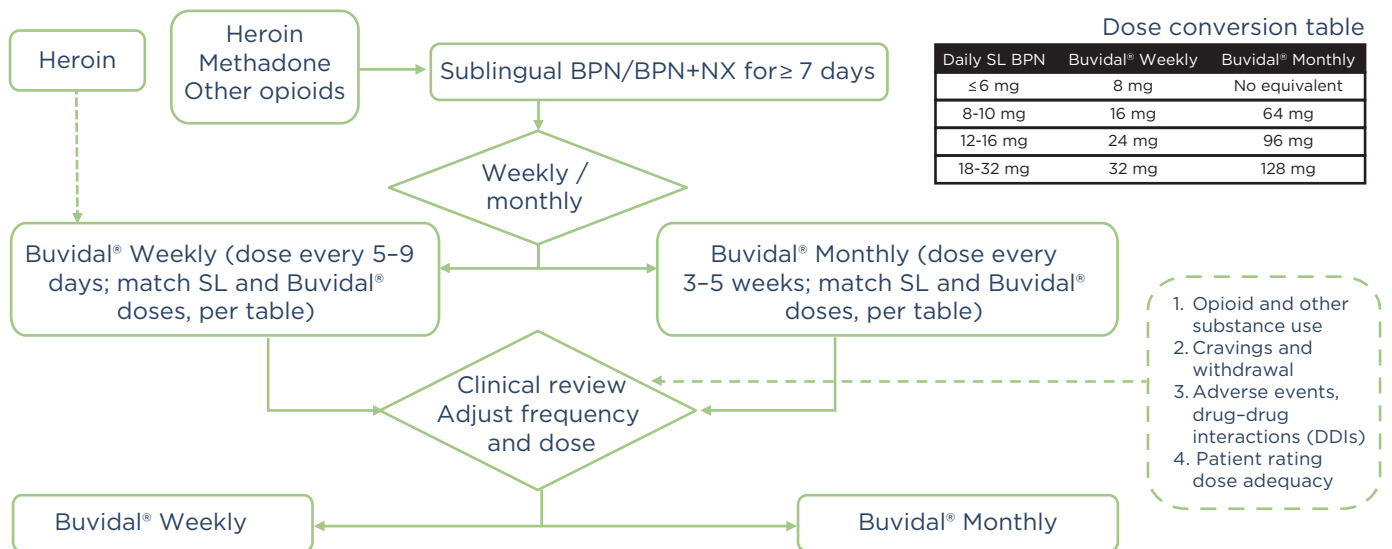
Patients may be switched from weekly to monthly dosing or from monthly to weekly dosing based on the recommendations in Table 5 sublingual and depot Buvidal® Weekly and Buvidal® Monthly doses above. Patients switching from weekly to monthly dosing will generally experience trough levels in the first few months similar to patients switching from SL BPN. Monitor patients for increased withdrawal or craving symptoms or other signs of instability. Individual titration to higher or lower doses may be required.

Whilst doses will be routinely scheduled to occur every 7 (Buvidal® Weekly) or 28 (Buvidal® Monthly) days, it is recognised that some

flexibility is required to accommodate missed appointments, travel, public holidays, appointment availability etc. To avoid missed doses, the weekly dose may be administered up to 2 days before or after the weekly time point (days 5-9), and the monthly dose may be administered up to 1 week before or after the monthly time point (weeks 3-5).

If a dose is missed, the next dose should be administered as soon as practically possible. If more than 10-14 days has occurred between doses of Buvidal® Weekly, re-induction may be required, with individual clinical titration. If more than eight weeks between Buvidal® Monthly has elapsed, re-induction may be required, with individual clinical titration.

**Figure 4 Overview dosing with Buvidal®**



**ii. Commencing treatment with Sublocade®**

Sublocade® treatment requires preceding treatment with SL BPN product for at least 7 consecutive days, preferably achieving SL doses ≥8mg daily. Longer periods of SL BPN treatment may be required prior to initiating depot BPN treatment if the patient reports BPN related adverse events or DDIs, has existing severe liver disease or is finding it difficult to stabilise on a dose of SL BPN.

The first Sublocade® dose should usually be administered approximately 24 hours after the last SL BPN dose. If a dose of SL BPN has been administered on the same day the dose of Sublocade® does not need to be delayed. The recommended dose of Sublocade® for most patients upon initiation is 300mg monthly for the

first 2 months (2 x monthly doses), reflecting 'loading' doses that elevate plasma BPN levels more rapidly in the initial treatment period.

There may be circumstances where treatment with Sublocade® may be initiated with 100mg (rather than 300mg) doses. Specifically, this arises in circumstances where there are safety concerns arising from hepatic impairment or DDIs (e.g. concomitant use other sedatives). It is recommended under such circumstances that the decision is discussed with the patient (e.g. patients should be made aware that even 100mg Sublocade® doses are significantly increasing plasma buprenorphine levels), documented in clinical notes, treatment effects are regularly monitored and the dose adjusted accordingly.

After the initial two 4-week doses of Sublocade® treatment, doses are flexible with either 100mg or 300mg SC injections every four weeks, decided by the physician in consultation with the patient. For most patients, 100mg monthly Sublocade® doses will be adequate, maintaining plasma levels (at steady state equilibrium) achieved with the first two 300mg Sublocade® doses, and is likely to be associated with fewer concerns regarding high dose BPN-related adverse events. Maintenance of 300mg doses should be considered for those patients who had previously stabilised on high dose SL BPN (e.g. 24 to 32mg daily), or continue to experience cravings or unsanctioned opioid use during the first 2 month period of Sublocade® dosing. Clinical titration is recommended, following the principles identified in section [Key principles in titrating depot BPN doses – adjusting dose and frequency of doses \(CS\)](#).

**a) Sublocade® flexible dosing schedules and missed doses**

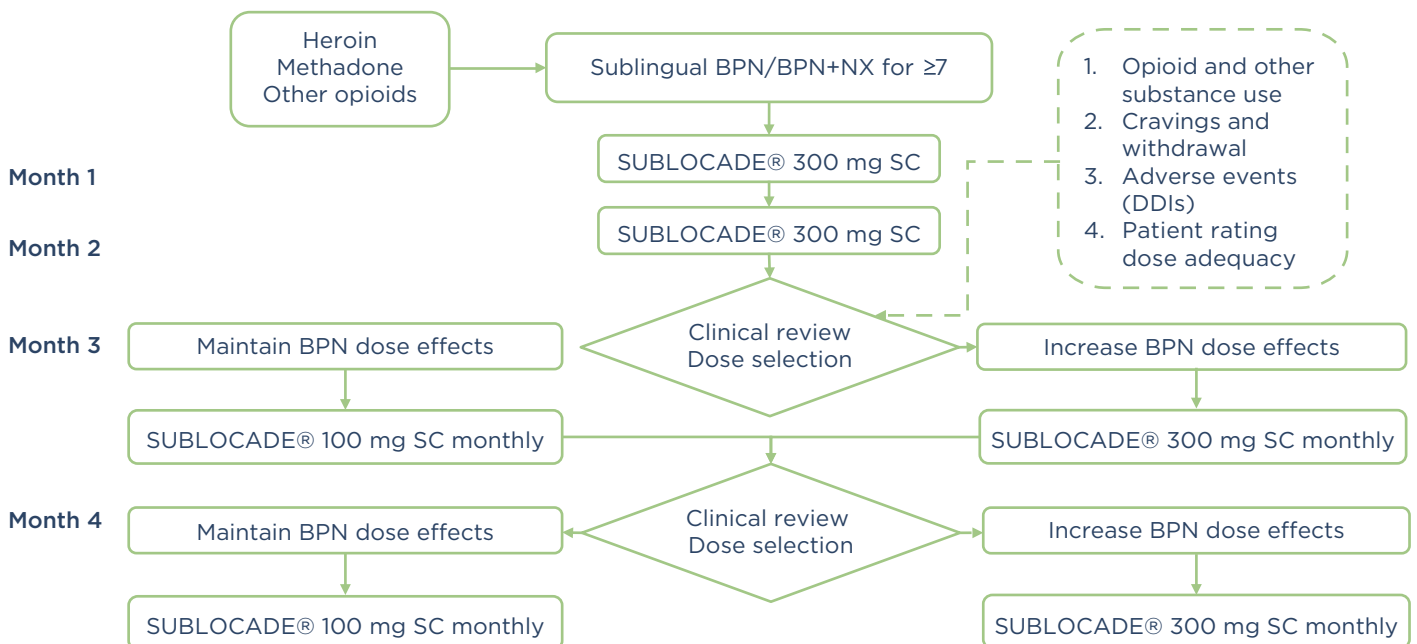
Whilst doses will be routinely scheduled to occur every 28 days, it is recognised that some flexibility is required to accommodate missed appointments, travel, public holidays, appointment availability etc. To accommodate such scenarios, Sublocade® doses can be administered up to 2 days ahead of a scheduled dose (i.e. 26 days since the last injection), or up to 14 days after the 28 day interval (i.e. to 42 days since the last injection) without dose adjustments.

Once steady state has been achieved (after two (300/100mg) and six (300/300mg) doses with Sublocade®), occasional delays in dosing up to 4 weeks (i.e. up to 56 days since the last injection) after the last scheduled dose are not expected to have a clinically significant impact on treatment effect, and therapeutic BPN plasma levels are generally maintained for this period of time. Dosing can usually be resumed without the need to alter the usual Sublocade® dose.

Delays in dosing of greater than 4 weeks (i.e. more than 56 days after last injection) may be associated with reduced plasma BPN levels and caution should be exercised in re-initiating treatment with Sublocade®. If there is any doubt regarding the patient’s opioid tolerance (e.g. patient reports experiencing opiate withdrawal features), then a test dose of SL BPN (e.g. 8mg) should be administered, and if there are no concerns (e.g. sedation), recommence Sublocade® dosing (on the previous 100mg or 300mg dose) the following day.

A patient who has had no documented and confirmed BPN doses for more than 56 days after their last injection, or has relapsed to regular use of heroin or other opioids since their last Sublocade® dose (with the attendant risk of precipitated withdrawal on recommencing BPN treatment), should be re-initiated to treatment with SL BPN for 7 or more days, before recommencing Sublocade® treatment.

**Figure 5: Overview dosing with Sublocade®**



### c. Key principles in titrating depot BPN doses – adjusting dose and frequency of doses (CS)

The following is a guide to depot BPN dose (Buvidal® and Sublocade®) selection beyond the initial doses:

- In general, doses should be maintained if:
  - the patient is achieving key treatment outcomes, such as no unsanctioned use of opioids, no clinically significant opioid withdrawal or cravings
  - there are no clinically significant dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, nausea)
  - the patient is satisfied with their current dose, and requesting the dose be maintained
- Doses should generally be reduced under the following conditions:
  - the patient reports BPN dose-related adverse events (e.g. sedation or lethargy, persistent headaches, nausea, elevated liver function tests)
  - the patient is seeking to reduce their dose in an attempt to ultimately withdraw from opioid agonist treatment
  - the patient is reporting the dose is ‘too high’ and/or is seeking a dose reduction, and there are no significant concerns regarding deterioration in clinical condition (e.g. substance use, physical or mental health symptoms) that may arise with a dose reduction.
- Dose should generally be increased under the following conditions:
  - The patient is not achieving desired treatment goals (e.g. persistent unsanctioned opioid use, opioid withdrawal symptoms or cravings)
  - the patient does not report dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, constipation, nausea, elevated liver function tests)
  - the patient reports their dose is too low and they would like a dose increase, and there are no significant clinical safety concerns

### d. Supplemental BPN dosing (CS)

In general, treatment with depot BPN should not routinely require additional or supplemental BPN dosing – wherever possible – depot doses should be adjusted (either the dose or frequency of administration) to ensure that patients are effectively and safely treated.

However, there may be circumstances where supplemental doses of BPN are required on a short term or interim basis until the next ‘usual’ depot BPN dose can be administered. Examples include:

- During dose titration in the early stages of depot treatment. For example, depot BPN doses are adjusted according to the patient’s prior SL dose, however, these transitional doses are a guide only, and subsequent dose adjustment may be required. Supplemental BPN doses may enable the patient to be held over until their next scheduled depot dose.
- Following drug-drug interaction – the commencement of another medication that induces hepatic metabolism of BPN (e.g. CYP 3A4 inducer such as carbamazepine) may cause BPN plasma levels to be reduced – resulting in features of opioid withdrawal, cravings or unsanctioned drug use.
- Delayed or interrupted depot dosing. Patients may miss their routine dose of depot BPN due to unforeseen circumstances – such as travel, transport problems, or other commitments. In some cases a dose of depot BPN can be organised to suit the conditions – however in other cases patients may not be able to access their routine depot dose on time. An interim period of treatment with SL BPN may be able to be organised instead – given it is more widely available in a range of community settings than the depot products.
- In response to other stressors or deterioration in psychological well-being. Some patients have a history of responding to a significant stressor by using substances. Sometimes, patients may request an increase in their methadone or BPN dose in order to cope without resorting to other substance use or harmful behaviours (e.g. aggression, gambling).



Whilst there may not be a strong pharmacological basis for altering OST doses under such circumstances, in practice this can be a useful short term measure to help patients through a difficult time, alongside working with and supporting the patient to develop alternative healthy non-medication coping skills.

It should be emphasised that patients should not be maintained for more than 14 days on SL BPN treatment in addition to depot BPN doses – adjustment of the next depot BPN dose is recommended. If patients persistently describe their depot BPN dose is not sufficient despite being on the maximum possible dose (e.g. 160mg Buvidal® Monthly or 300mg Sublocade®), then consider either transferring to the other depot formulation (the delivery system may make a difference), or consider discontinuing depot treatment and resuming SL BPN or methadone treatment.

### **i. Supplemental dosing for patients treated with Buvidal®**

The preferred approach to supplemental dosing for patients treated with Buvidal® (for which there is the most clinical experience and available safety data) is to use supplemental doses of Buvidal® (e.g. 8mg weekly top-up doses) to hold a patient until their next scheduled regular dose, and then to adjust the next Buvidal® dose accordingly.

However, where supplemental Buvidal® depot injections cannot be used (e.g. no access to product), then additional doses of SL BPN (+/- naloxone) tablets/film) should be prescribed – either to add to (or ‘top up’) existing Buvidal® (in which case use up to 8mg SL BPN per day); or SL BPN doses can be used ‘instead of’ Buvidal® (e.g. missed Buvidal® doses and SL BPN required until next Buvidal® can be administered – in which case SL BPN doses should be guided by Table 5 sublingual and depot Buvidal® Weekly and Buvidal® Monthly doses). Consult with an Addiction Medicine specialist for further advice if required.

### **ii. Supplemental sublingual dosing for patients treated with Sublocade®**

Whilst patients generally do not require additional doses of BPN during treatment with Sublocade®, short term (up to 14 days) supplementary doses of SL BPN (SL BPN +/- naloxone tablets/film) of no more than 8mg daily can be prescribed as ‘rescue doses’ until the next scheduled dose of Sublocade®.

In circumstances of a missed Sublocade® dose and where the patient is reporting features of opiate withdrawal or cravings, then doses of SL BPN may be used until the next dose of Sublocade® can be administered (e.g. using 8mg SL BPN per day, and titrating the dose accordingly).

### **e. Transfer between Buvidal® and Sublocade® (CS)**

Generally, transferring patients between Buvidal® and Sublocade® should generally be avoided – there is no published data or clinical experience to provide recommendations on transfer between Buvidal® and Sublocade® products. Swapping patients back and forth between Buvidal® and Sublocade® unnecessarily should be avoided.

However, situations may occur where it is not possible to continue one formulation, and transfer to the other depot may be clinically preferable to transfer back to SL BPN. Circumstances when transfer between Buvidal® and Sublocade® may include:

- Lack of availability of the formulation the patient had been treated with at the new treatment site (i.e. the treatment site only has one formulation – Buvidal® or Sublocade®, and the patient had been treated with the other formulation).
- Interrupted supply of one formulation (i.e. the formulation the patient had been treated with is not available when required).

If transfer between formulations does occur, in the absence of clinical studies on transfers between Buvidal® and Sublocade®, the following recommendations have been developed, based on pharmacokinetic and clinical data.

See Figure 1 Pharmacokinetic parameters – steady state for data on C<sub>max</sub>, C<sub>min</sub> levels of BPN following depot administration at steady state.

#### **i. Transfer from Sublocade® to Buvidal®**

Patients on stable Sublocade® 300mg monthly doses should transfer to Buvidal® Weekly 32mg or Buvidal® Monthly 128mg. Patients may experience a decrease in serum BPN levels and may experience opiate withdrawal and/or cravings following transfer to Buvidal®, although this is unlikely to occur given the long half-life of Sublocade®.

Patients on steady Sublocade® 100mg monthly doses should not experience a significant decrease in serum BPN levels when transferring to Buvidal® Weekly or Buvidal® Monthly. Commence at Buvidal® Weekly 24 mg or Buvidal® Monthly 96 mg and titrate doses up or down as clinically indicated.

## ii. Transfer from Buvidal® to Sublocade®

Patients on Buvidal® Weekly or Buvidal® Monthly should be transferred to 100mg Sublocade® doses. In most cases, as the patient already should have adequate BPN plasma levels, the two 300mg 'induction' Sublocade® doses should not usually be required. If patients experience significant opioid cravings or withdrawal on this regimen, titrate up to the Sublocade® 300mg dose (see section on *Key principles in titrating depot BPN doses – adjusting dose and frequency of doses (CS)*).

## f. Induction from other opioids: prescription opioids and methadone

Patients should be initiated onto at least 7 days of SL BPN treatment prior to initiating depot BPN treatment. Longer periods of SL BPN treatment may be required if the patient reports adverse events, drug-drug interactions or if finding it difficult to stabilise on a dose of BPN – for example following a transfer from methadone (which can take 1-2 weeks to stabilise). Guidance on initiating SL BPN treatment from other opioids (including prescription opioids and methadone) can be found in National Guidelines for Medication Assisted Treatment of Opioid Dependence (2) (Section A.4).

## g. Administering depot BPN injections

Buvidal® Weekly and Buvidal® Monthly and Sublocade® administrations are intended for subcutaneous use only. There should be sufficient subcutaneous tissue to allow for the injection. The area should be free of scarring, nodules or other lesions and not be inflamed, infected or bruised. A slow steady push should be used as slower injections are generally better tolerated. See the product information for details.

Injections should only be by an Australian Health Practitioner Regulation Agency (AHPRA) registered healthcare professional who has injection of schedule 8 medications within their scope of practice.

**Depot BPN should never be administered intramuscularly, intra-dermally, intravenously or intra-arterially.** Serious health risks (including pulmonary thrombosis, infections, tissue necrosis) may occur if depot BPN is not injected as advised.

## i. Administering Buvidal® injections

Buvidal® Weekly and Buvidal® Monthly should be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Injection sites should be rotated. The injection sites may be alternated between the different injection areas i.e., the buttock, thigh, abdomen, or upper arm. The actual angle of injection will depend on the amount of subcutaneous tissue however Buvidal® should usually be administered at 90 degrees. Detailed instructions for use refer appendix *Buvidal® Weekly product information AUS / Buvidal® Monthly product information AUS*.

## ii. Administering Sublocade® injections

Sublocade® should be injected subcutaneously in the abdominal region between the transpyloric (Addison's) and transtuberular planes. Injections should be given with the patient laying down. Injection sites should be rotated. The actual angle of injection will depend on the amount of subcutaneous tissue however Sublocade® should usually be administered at 45 degrees. Refer appendix [Sublocade® product information AUS](#).

Sublocade® must be administered at room temperature. It may take 15 minutes after removing Sublocade® from refrigeration to achieve this temperature (30).

## h. Specific issues of delivering OAT with depot BPN

### i. Intoxicated presentations

Patients presenting intoxicated at the time of dose administration should be assessed to identify any safety concerns regarding dosing. Peak plasma and clinical effects occur approximately 12-24 hours after Buvidal® Weekly depot injections, 6-10 hours after Buvidal® Monthly and 24 hours after a Sublocade® injection, and hence there is usually

little clinical indication to withhold a depot injection due to a patient presenting intoxicated, in contrast to intoxicated presentations for SL BPN or methadone dosing, where peak medication effects are likely to occur whilst the patient is still intoxicated. Patients should however be assessed as having capacity to provide informed consent to their usual dose, and to understand warnings regarding risks of sedation and overdose from polysubstance use. If there are concerns that the patient is very intoxicated and unable to understand or follow instructions, the administration of the dose may be deferred and rescheduled.

## ii. Transfer of care

Particular attention is required when communicating with other health care providers regarding transfer of care for patients treated with depot BPN. Many health care providers will initially be unfamiliar with the new Depot BPN formulations (or confuse Buvidal® and Sublocade® BPN formulations), and may not be familiar with the prolonged dosing intervals.

When transferring care or providing clinical handover to other health care providers, ensure the following is communicated clearly:

- Details of service providers prescribing and administering depot BPN injections and previous injection sites (in order to avoid injecting into same site)
- Dose and date of recent depot BPNs ensuring details of last dose administered are included
- The formulation of depot BPN that was administered: Buvidal® Weekly, Buvidal® Monthly or Sublocade® and the dose (in mg)
- Scheduled next dose of depot BPN (formulation, date, dose strength and route of administration),
- Any adverse events, risks or concerns regarding depot BPN treatment that is relevant to other health care providers

As depot BPN treatment is new, untrained service providers may be unfamiliar with the treatment model or doses used, and ensure that differences in the doses, frequency of administration and dispensing conditions are understood by the new providers.

As depot BPN medication may not be easily administered during a brief inpatient hospital admission, it is possible that it can be erroneously omitted from hospital discharge summaries and medication reconciliation procedures. Treatment providers should endeavour to ensure that BPN treatment is accurately documented in transfer of care documentation and related clinical handover activities.

## i. Prescription charting

Prescribers must ensure that all prescriptions for depot BPN are legally written, and compliant with local jurisdictional regulations for S8 opioid medications (NSW – Poisons and Therapeutic Goods Regulation 2008).

In order for a prescription of depot buprenorphine to be valid it must include prescribing doctor's details (name, Prescriber Number, contact details), patient's details (name, address), Name of buprenorphine product (e.g. Buvidal® Weekly; Sublocade®); the dose (in numbers and words), route of administration, and number of doses to be administered. We recommend that the prescriber document that the dose should be dispensed to a health care provider and never directly to the patient or their carer.

# 5.

## Discontinuing depot BPN treatment

### Potential scenarios for discontinuing depot BPN treatment are possible

- a. Withdrawing off depot BPN (with goal of opioid abstinence)
- b. Transfers to SL BPN
- c. Transfer to methadone / other opioid analgesics
- d. Transfer to oral naltrexone

### a. Withdrawing off depot BPN (with goal of opioid abstinence)

Many patients in OAT are keen to achieve abstinence, discontinue opioid treatment and withdraw from opioids. Unfortunately, most patients attempting withdrawal from OAT relapse to unsanctioned opioid use and are at increased risk of opioid overdose with as few as 10-20% of patients successfully achieving opioid abstinence in the short to medium term. Whilst some patients describe withdrawal from SL BPN treatment as ‘shorter’ and ‘easier’ than methadone withdrawal, there is little evidence to indicate greater longer term success rates with either medication. A better prognosis for successful withdrawal from OAT is achieved for patients who: have been able to stop using illicit/non-prescribed opioids; do not have other significant substance use problems; have been able to make lifestyle changes to support ongoing cessation of opioid use (e.g. employment, education, supportive relationships), gradual rather than precipitous reduction regimens on methadone or BPN. These conditions are most likely relevant for patients attempting withdrawal from depot BPN treatment also.

There is very little experience and no studies examining withdrawal from depot buprenorphine treatment. The onset, peak and duration of withdrawal symptoms is likely to be variable between patients, and according to the duration of prior depot BPN dosing. In general, withdrawal syndrome from depot BPN is expected to occur several weeks to several months after the last dose, persist for longer, and may be of lower severity than withdrawal from SL BPN.

The withdrawal time course and severity has not been characterised for the depot BPN products. Table 6 Timeframe serum BPN undetectable highlights the time frame that serum BPN levels drop to sufficiently low levels for the emergence of significant withdrawal features withdrawal symptoms are expected to occur following long term (steady state) depot BPN doses – although one may expect considerable individual variability.

**Table 6: Timeframe serum BPN undetectable following discontinuation of long term depot BPN treatment**

Depot BPN	Half-life (at repeated doses)	Likely timeframe for onset of withdrawal symptoms after last maintenance depot dose
Sublocade® 300mg doses,	43 to 60 days	3-9 months
Sublocade® 100mg doses	43 to 60 days	2-6 months
Buvidal® Weekly	3-5 days	Up to 2-3 weeks after last dose
Buvidal® Monthly	19-25 days	Up to 2-3 months after last dose

Patients who have been on treatment for long enough to achieve steady state plasma levels of depot BPN are likely to have a longer time course of reduction of BPN levels and therefore longer time course of withdrawal symptoms than those on depot BPN treatment for shorter periods.

Wherever possible, patients should reduce their depot BPN dose prior to discontinuing dosing. This could include:

- For patients on Buvidal® Weekly, reducing to the 8mg weekly dose before ceasing depot BPN
- For patients on Buvidal® Monthly, reducing to the 64mg dose before ceasing depot BPN
- For patients on Sublocade®, reducing to the 100mg dose before ceasing depot BPN

As in attempts to withdraw from other forms of OAT, clients and treatment plans should be reviewed regularly, with additional psychosocial supports to maintain motivation, and cope with cravings, withdrawal and the risk of relapse. There may be a role for symptomatic medication to assist with features of opioid withdrawal ((2) Section A4), however caution should be used in using extended use (beyond a few days) of sedatives or hypnotic medications. Patients who have withdrawn from depot BPN should be strongly encouraged to access supplies of take home naloxone.

## b. Transfers to SL BPN (CS)

Given the variable excretion and clinical effects of depot BPN products – there can be considerable individual variation in when the clinical effects of prior depot BPN treatment subside. This will be affected by prior depot dose (generally longer effects with higher doses), duration (generally longer effects with long-term depot treatment), variation in hepatic function, age, and the patient’s sensitivity to withdrawal symptoms, cravings and other stressors.

### i. For Sublocade® to SL BPN

Recommended practice is to initiate SL BPN with low doses at approximately the time of the next scheduled depot BPN injection – usually commencing with 8mg SL BPN four weeks after the last Sublocade® dose, and to titrate the dose upwards over subsequent days or weeks according to clinical need (features of withdrawal, craving, intoxication, use of unsanctioned drugs) as the depot BPN concentrations gradually subside, aiming to achieve the expected SL dose based on dose conversion tables. Frequent clinical reviews are recommended.

### ii. For Buvidal® to SL BPN

Initiate SL BPN dosing at the time of the next scheduled injection (e.g. 5-9 days after Buvidal® Weekly, or 3-5 weeks after last Buvidal® Monthly injections). Dose conversion tables should be used to guide the initial SL BPN dose, with frequent clinical reviews in order to titrate the SL dose over subsequent days.

**Table 7: Sublingual and depot Buvidal® Weekly and Buvidal® Monthly doses**

Buvidal® Weekly depot dose	Buvidal® Monthly depot dose	Daily SL BPN dose
8mg	No monthly equivalent	≤ 6mg
16mg	64mg	8-10mg
24mg	96mg	12-16mg
32mg	128mg	18-32mg

It should be emphasised that there remains a relative lack of experience in transferring patients from depot to SL BPN – and faster response times, or higher or lower doses than those suggested above may be required. Patients should be reviewed regularly and doses titrated according to clinical need, and clinicians should document the rationale for their decision-making.

## c. Transfer to methadone or other opioid analgesics (CS)

There is little clinical experience and no published studies regarding transfer from depot BPN to methadone. Given this lack of evidence, patients seeking to transfer from depot BPN to methadone should transition via SL BPN, (as described in previous section). Once stabilised on a dose of SL BPN for at least 2 weeks (for Buvidal® Weekly) and 4 weeks (for Buvidal® Monthly or Sublocade®), transition to methadone can occur, as described in the NSW Clinical Guidelines: Treatment of Opioid Dependence (1) initiating at low doses 20-30mg daily, reviewing regularly and titrating accordingly).

If a patient has to discontinue all BPN treatment abruptly (e.g. due to a severe AE, or patient unwillingness to continue any BPN treatment), transition to methadone can be considered after consultation with an addiction specialist. The general principle is to recommence low dose methadone (e.g. 20mg oral daily doses) at the time of the next proposed depot dose, regularly monitor the patient (at least weekly), and carefully increase the dose (by no more than 5mg intervals) after clinical reviews until the methadone dose and patient have stabilised, recognising that residual BPN from depot BPN doses may be present for up to 4-6 months after long term treatment with Sublocade® 300mg, or 2-3 months after 100mg Sublocade® or Buvidal® Monthly treatment.

#### d. Transfer to oral naltrexone (CS)

Transfer to oral naltrexone should be possible after BPN effects have subsided – generally 2-4 weeks after weekly depot BPN and 4 to 12 weeks after the last dose of monthly depot BPN (but possibly up to 6 months for patients who have been on 300mg Sublocade® doses). The risk of precipitated withdrawal under these circumstances is considerable, and transfer should generally be undertaken in an inpatient setting or under close observation, following a urine drug test negative for opioids, and ideally a negative naloxone challenge test. Low NTX doses should be initiated (e.g. 12.5mg daily), increasing by 12.5mg per day until the target dose of 50mg daily is achieved. Consult with a specialist if any concerns.

# 6.

## Clinical conditions

### a. Overdose

Whilst BPN on its own is rarely associated with overdose in dependent opioid users, overdose can occur in the context of polydrug use, specifically the use of other sedatives such as alcohol and benzodiazepines. Under such circumstances, emergency treatment is required with supportive care (oxygen therapy, assisted breathing and recovery position) and the use of naloxone. Whilst laboratory studies (animal and receptor binding studies) suggest that very high doses of naloxone (e.g. 10mg IM/IV) are required to reverse the effects of BPN (due to the comparable affinity of BPN and naloxone for the mu opioid receptor), in practice, polydrug overdoses in which BPN is implicated generally respond to routine doses of naloxone (e.g. 1-2mg IM/IV).

The specific potential risks of the depot BPN product are the prolonged plasma levels of BPN, rather than higher plasma levels compared to sublingual dosing. Hence, we expect no greater risk of overdose occurring from depot BPN formulations, however the prolonged duration of BPN effects with depot formulations requires patients to be clinically monitored for extended periods of time, until the patient has clinically recovered, and may require prolonged monitoring and a naloxone infusion in a hospital setting.

Note that depot BPN (Buvidal® and Sublocade®) must be administered as a subcutaneous injection. Intravenous administration requires close monitoring in a hospital setting monitoring for phlebitis/local injection reaction, swelling and associated impaired arterial supply, pulmonary emboli and overdose.

### b. Polydrug use and regular intoxication

The issue of administering depot BPN doses to an intoxicated patient is addressed in section [Specific issues of delivering OAT with depot BPN](#). Specific interventions may be required for patients with harmful patterns of other substance use – such as alcohol, benzodiazepine, stimulants, cannabis and/or injecting drug use. These are described in National Guidelines for Medication Assisted Treatment of Opioid Dependence (2). Patients with patterns of regular and harmful substance use often benefit from regular clinical monitoring and review, which may be more difficult to schedule in patients attending for dosing only once a month. If more frequent clinical reviews are required and the patient has a history of non-attendance for scheduled appointments, then a medication option with a more frequent dosing interval may be considered. Patients with heavy and regular/ dependent patterns of use of alcohol, benzodiazepines and stimulants (and other psychoactive substances) may require specific interventions aimed at reducing/ceasing use of those substances including drug counselling and/or withdrawal and ongoing support.

### c. Acute pain management in patients in depot BPN treatment

Patients on opiate agonist treatment frequently encounter episodes of acute pain that require management, which can be complicated by buprenorphine treatment nevertheless there are approaches for pain management and it is important that patients have access to effective pain management.

BPN has high mu receptor affinity and reduces the effects of most full opioid agonists such as morphine or oxycodone. Whilst this has little impact on the management of mild acute pain (where NSAIDs or paracetamol and physical therapies may be considered), BPN can complicate routine opioid analgesia in the management of

severe acute pain (e.g. in acute/emergency situations such as trauma, renal stones). It is important that patients' acute pain is effectively managed and in such circumstances, the National Guidelines for Medication Assisted Treatment of Opioid Dependence (2) recommend the following approaches (a) use of higher doses of traditional opioids such as morphine (with careful titration of effects); (b) use of mu opioid receptor super agonist such as fentanyl that themselves have higher mu intrinsic activity than BPN; and/or c) use of non-opioid analgesic approaches such as ketamine infusions or regional analgesia.

Similar approaches can be used for patients with depot BPN treatment to achieve analgesia in acute/emergency situations. It is not possible to reverse or cease BPN plasma levels in patients treated with depot BPN formulations without surgical removal of the depot BPN.

#### **d. Chronic pain management in patients in depot BPN treatment**

Chronic pain is common amongst patients in OAT (estimated at between 30 to 60% of patients), and is often managed or 'masked' by the high doses of methadone or BPN used to treat opioid dependence. Whilst current evidence does not identify the most effective strategies for treating chronic pain in patients in methadone or BPN treatment, general principles of chronic pain management should be followed (33), and include patient education and engagement in the treatment process, appropriate use of opioid and non-opioid medications (e.g. antidepressants, NSAIDs, paracetamol, gabapentanoids), physical (e.g. exercise, physiotherapy) and psychosocial (e.g. Cognitive Behavioural Therapy) interventions. BPN itself is a powerful opioid analgesic, and extended release BPN formulations (e.g. 7-day topical patches) have historically been incorporated into treatment plans for patients with concurrent chronic pain, and it is expected that depot BPN formulations will also be effective as part of treatment plans in managing comorbid chronic pain in dependent opioid users. BPN should not be used in conjunction with other opioid analgesics (e.g. morphine, fentanyl, codeine) in chronic pain management, given the 'blockade' effects of depot BPN.

There is no evidence currently available comparing high dose sublingual and depot BPN formulations in chronic pain management.

#### **e. Surgical removal of depot BPN**

Data on surgical removal of Buvidal® is not available.

In the event the depot Sublocade® dose must be removed, it can be surgically excised under local anaesthesia within 14 days of injection. Only the most recently-injected depot can be removed. The surgical procedure requires a small incision in the abdomen where the depot was placed, removal of the depot with forceps, and suturing to close the incision. The removed depot should be handled with adequate security, accountability, and proper disposal, according to facility procedure for a Schedule 8 drug product and pharmaceutical biohazardous waste, and per applicable federal, state, and local regulations. The residual plasma concentrations from previous injections will decrease gradually over subsequent months. Patients who have the depot removed should be monitored for signs and symptoms of withdrawal and treated appropriately (30).



# 7.

## Use of depot BPN for withdrawal treatment

There is considerable interest among patients and clinicians in the use of long-acting depot BPN formulations to assist in withdrawal from opioids such as heroin or methadone, given their long duration of action, gradual taper of BPN plasma levels, and logistic simplicity (e.g. one single dose without need for daily dosing). The gradual taper over days (for Buvidal® Weekly) or weeks (Buvidal® Monthly, Sublocade®) may be well suited to assisting patients in their attempts at opiate withdrawal.

However, at this time there is little clinical experience or research evidence to inform the use of depot BPN for managing opiate withdrawal, and further research is required. Consultation with a suitable addiction specialist is recommended.

# 8.

## Special populations and settings

### a. High risk or vulnerable populations

There are a range of health conditions (e.g. cognitive impairment, severe psychiatric conditions, poor mobility), social circumstances (e.g. child protection concerns, domestic violence, homelessness, poor literacy, social isolation) and demographic backgrounds (Aboriginal and Torres Strait Islander people, culturally diverse backgrounds, women, LGBTI people, culturally diverse communities, prisoners, older people) that can greatly impact upon the experience of engagement of clients with opioid treatment (and other service) providers. The introduction of depot BPN treatment that allows for dosing on a monthly basis may enhance patient autonomy in some cases, alternatively may detract from the ability to engage the client with treatment and other services. Particular attention to informed consent to treatment with depot formulations is required, and consumer workers or advocate services should be available. Service providers and clients should collaboratively implement strategies that aim to enhance attendance for dosing and clinical reviews, and consider active follow-up strategies for clients who do not attend for scheduled appointments.

#### i. Aboriginal people

To address the significant health burden affecting the lives of Aboriginal people, it is important to consider their unique cultural and health needs when providing treatment and care. The aim is to provide a variety of treatment options to reflect the diversity of Aboriginal people, to maximise their health, wellbeing and social functioning, as well as to reduce risk to community safety and health with a culturally safe approach. This is especially relevant given the substantially higher rates of mortality and morbidity experienced by Aboriginal people compared to other Australians.

Existing mainstream models of practice in the drugs and alcohol field have been developed primarily within western systems of knowledge and may ignore an Aboriginal 'worldview'.

Application of these models to working with Aboriginal people can be detrimental, to the extent that some approaches can directly undermine cultural ways of working. This can affect Aboriginal people's engagement with, and experience of, the health system and impact on their decisions to seek support and treatment.

Models of drug and alcohol treatment, which are framed from within an Aboriginal cultural context and developed by Aboriginal people, are likely to be more effective. Such models respect the legitimate rights, values and expectations of Aboriginal people and acknowledge the diversity within and between Aboriginal communities living in remote, regional and metropolitan areas. These models:

- incorporate an Aboriginal holistic concept of health and wellbeing;
- are grounded in an Aboriginal understanding of historical factors, including traditional life, the impact of colonisation and the ongoing effects;
- aim to strengthen Aboriginal family systems of care, control and responsibility;
- address culturally appropriate approaches to harm reduction; and
- work from within empowerment principles.

For resources on health issues for Aboriginal people, see [www.healthinonet.ecu.edu.au](http://www.healthinonet.ecu.edu.au)

### b. Hospital and correctional settings

Many patients in OAT have brief episodes of admission to hospital or correctional facilities (e.g. remand, police lock-up) that result in interruptions in methadone or BPN dosing. It is expected that this will be less of a concern with depot BPN treatment. Nevertheless, careful co-ordination between hospital and correctional staff with depot BPN treatment providers will be required.

## **i. Correctional settings**

Depot BPN has a number of potential benefits as a treatment option in the correctional setting. Diversion of SL BPN is commonplace in prisons and is associated with interpersonal violence as well as viral and non-viral injecting related injuries and diseases (IRID). The subcutaneous formulations have less capacity for diversion.

Administration of SL BPN in prisons is time intensive, with individual patients taking 10-20 minutes for films to dissolve, requiring considerable time resources for both correctional officers and health staff. Once a month administration of depot BPN will allow increased time for patients to receive other health interventions.

The period immediately following release from custody is a high risk period for patients, with 3-8 times risk of overdose death. It is often challenging for patients to attend OAT dosing on the first day after release due to geographic, housing, social and financial reasons. A depot preparation may provide greater stability over this period with less urgency for immediate attendance. This may be beneficial for both the patient and community treatment teams.

Up to 25% of patients on OAT in NSW Correctional Centres are released into the community unexpectedly via courts (outside control of health). Depot BPN having longer dosing windows may allow greater flexibility to arrange community dosing and provide transfer of care documentation. Patients on depot BPN leaving custody should be provided education re the persistent clinical effects depot BPN.

As depot BPN may take several doses to reach steady state, transfer of care documentation both on entry into custody and on release will require detailed documentation of doses given over a period several months.

## **c. Residential rehabilitation and supported housing settings**

Historically many alcohol and other drug residential rehabilitation programs or supported housing providers (e.g. nursing homes) have not been able to support patients in OAT due to concerns regarding methadone or BPN dispensing or storage of take-away doses. Treatment with depot BPN provides an opportunity for OAT to be better integrated into these settings, with either the patient attending the dosing site or, if possible, the depot BPN service providers attending the rehab/housing service.

# 9.

## Managing travel

Patients must not be supplied with Buvidal® or Sublocade®. Depot BPN must only be handled by a healthcare professional after delivery to a clinic/administration site.

### a. Local travel

The duration of action of depot BPN should make local travel less problematic for patients. For information on doses that need to be given before/after the scheduled date see section [Buvidal® flexible dosing schedules and missed doses](#), [Sublocade® flexible dosing schedules and missed doses](#).

### b. Interstate transfer

See section 3.5 Prescriber related information of the NSW Clinical Guidelines: Treatment of Opioid Dependence (1) re interstate transfers. Beyond interstate sites having access to Buvidal® and/or Sublocade®, there are no additional requirements.

### c. Overseas travel

As Buvidal® and Sublocade® cannot be given to patients, overseas travel will require transferring patients back onto sublingual treatment if the travel duration is more than five weeks for Buvidal® Monthly or six weeks for Sublocade®. Dose titration of the required sublingual dose should occur before travel commences so patients can be observed during transfer from depot BPN to SL BPN.

At the time of writing:

- Sublocade® is registered and available in the US
- Buvidal® is registered in the EU and has been launched as per January 2019.

# 10.

## Patient information and perspective (NUAA)

Depot buprenorphine should always be presented as one choice in the range of currently available OTP medications – patients may need a great deal of information and reassurance from their clinicians as they assess whether depot buprenorphine will be compatible with their lifestyles and where they are in their treatment journeys.

This support will need to continue if they make a decision to transition to depot buprenorphine. No matter the advantages of the new mode, the depot injection is a leap in the dark that for many patients will signify a relinquishment of control. Until the first dose has run its course without problems, a patient cannot be totally comfortable that they have made the right decision.

There will be patients who wish to transition from sublingual buprenorphine as well as patients on methadone or Biodone who will be interested in the pathway to depot buprenorphine. All patients will need to know how this OTP medication is similar to, and different from, the formula they are currently taking, and what is involved in transitioning.

The decision process and transitioning phase should occur within a co-operative therapeutic relationship that balances a clinician's medical expertise and knowledge with a patient's treatment goals as the expert in their own life.

Patients need to be armed with a wide range of information about depot buprenorphine. The sorts of things that patients will want to know include:

- product pharmacology profile, effectiveness and safety including half-life and average peak/trough patterns, control of cravings and any pleasure aspect
- prescribing and dosing procedures including dose amounts, duration of effect and insertion routines
- the way transfer from other OTP medications will take place and if they will experience withdrawal symptoms

- options for managing side effects, chronic and acute pain and exiting the program
- any other problems that might arise and how they might be addressed
- their rights and responsibilities
- expected financial outlay.

As a clinician, you can champion agency and choice in your relationship with your patients by:

- recognising that this new product will suit some but not all people currently on the program and that a choice of a range of OTP medications is an essential health response
- listen to, take seriously and act promptly when your patients describe their experience – that the medication is not holding them or that they are experiencing side effects. We're all new at this, don't hesitate to call clinician information lines for support
- listening to people's stories, goals, challenges and expectations
- advising and guiding your patient to assist them get the best OTP fit for them
- encouraging them to compile a list of advantages and disadvantages to help them with their decision-making
- offering a move to depot bupe as a trial, reassuring your patient that they will be able to return to sublingual bupe or methadone liquid if depot bupe does not suit them
- respecting your patient's decision to not try depot bupe, even if their objections seem irrational
- making sure the patient has sufficient harm reduction information if they do not want to be abstinent from all illicit drugs, with special attention to overdose risks and reversal.

There are many patients who will find depot buprenorphine fits well with their treatment goals, but because they may have less contact with prescribers and/or dosing agencies, they may need support that is different from patients on other OTP medications. You can set your patient up for success by:

- discussing your expectations for how the therapeutic relationship will need to operate to maximise the usefulness of depot buprenorphine
- encouraging frank communication with your patient
- making clinical decisions that do not discriminate, punish or reward but rather provide professional responses to any clinical challenges that might arise
- working with your patient to prepare or review and amend their treatment plan and goals including discussing expectations around exiting the program
- talking through options around treatment outside of dosing contact (counselling etc.),
- reassuring your ongoing support and connection, especially if the patient is moving from very regular contact with an OTP service
- explaining that they should not drive or operate heavy machinery while they are getting used to the new formulation, or after a dose change until their prescriber advises they can do so
- encouraging patients to think about how they will fill in their time positively, in a way that helps them move forward, become healthier and improve self-esteem
- making sure patients have access to the consumer guidelines for the OTP and any of the several special interest guides, including the guide to depot buprenorphine.

Many clinicians will treat patients with particular needs. Being sensitive to the diversity of OTP patients may include:

- Being aware that some cultures will have restrictions around the gender of the person who can give them an injection
- Being aware that there may be cultural issues around injecting in particular sites
- Understanding that using a professional interpreter is always preferable to using a family member, for clearer, unbiased and confidential exchange of information
- Staying abreast of how the OTP operates in jails and recognising that some consumers transferring from jail may need different OTP responses in the community than they did in jail.

All in all, the best therapeutic relationships are built on co-operation, unbiased information sharing and an honest and open exchange that balances your clinical responsibilities with your patient's treatment goals.

# 11.

## Governance issues

### a. Acquisition

A registered medical practitioner can obtain depot BPN from a licensed wholesaler on a signed and dated order (on the letterhead) of the medical practitioner. Provision is also made to order stock electronically or by telephone from a licensed wholesaler, providing that a signed confirmation of order and receipt of order is returned to the licensed wholesaler after delivery of the stock.

### b. Storage

#### i. Buvidal®

Buvidal® injections are required to be stored below 25°C. Do not refrigerate or freeze. To comply with the Poisons and Therapeutic Goods legislation, as for all Schedule 8 drugs, Buvidal® injections must be kept apart from all other goods (other than cash or documents) in a safe, cupboard, or drawer in a cabinet, which is securely attached to a part of the premises, and which is kept locked when the drug is not in immediate use.

#### ii. Sublocade®

Sublocade® injections are required to be stored refrigerated at 2 – 8°C. The storage must meet the following requirements to comply with the Poisons and Therapeutic Goods legislation,

- the refrigerator must be in a room (which includes a part of a room or an enclosure) to which the public does not have access,
- the refrigerator, or any cupboard or receptacle in which the refrigerator is kept, must be securely attached to a part of the premises,
- the refrigerator, or the room, cupboard or receptacle in which the refrigerator is kept, must be kept securely locked when not in immediate use
- the refrigerator must not be used to store any other item that is not a substance listed in Schedule 2, 3, 4 or 8 of the Poisons List or is not a therapeutic good

Once outside the refrigerator this product may be stored in its original packaging at room temperature, less than 25°C, for up to 7 days prior to administration. Once outside the refrigerator, Sublocade® injections must be kept apart from all other goods (other than cash or documents) in a safe, cupboard, or drawer in a cabinet, which is securely attached to a part of the premises and which is kept locked when the drug is not in immediate use. Discard Sublocade® if left at room temperature for longer than 7 days.

### c. Accountability

A medical practitioner must make record of all buprenorphine depot injections obtained from the wholesaler or administered to the patient in a drug register.

A drug register must be in the form of a book:

- a) that contains consecutively numbered pages, and
- b) that is so bound that the pages cannot be removed or replaced without trace, and
- c) that contains provisions on each page for the inclusion of the particulars required to be entered in the book.

On the day on which the medical practitioner receives or administers buprenorphine at the clinic, the medical practitioner must enter in the drug register for that clinic the following particulars:

- the date of receipt or administration
- the name and address of the supplier (in the case of receipt) or the name and address of the patient (in the case of administration or supply)
- the quantity received or administered and the balance held after the transaction; and
- the signature of the medical practitioner

A separate page in the drug register must be used for each brand and each strength of the buprenorphine injection. No alteration may be made in the register, but any mistake may be corrected by a marginal or footnote, initialled and dated by the medical practitioner. The register must be kept on the premises in which the buprenorphine injections are stored. The register must be retained for a period of two years from the date of the last entry and must be made available for inspection if required.

Twice a year, during March and September, medical practitioners must carry out a full stock check of all drugs of addiction in their possession. However, it is recommended that a full stock check is undertaken on a regular basis (eg monthly) Immediately under the last entry for each drug in the drug register, they should write the date on which the check was done, the words “Balance on hand”, the quantity actually held, and they should sign the entry.

If the drug register is lost or destroyed, the medical practitioner must immediately:

- notify the Ministry of Health in writing of the fact and of the circumstances. The notification should be addressed to:  
Director  
Pharmaceutical Regulatory Unit  
NSW Ministry of Health  
Locked Mail Bag 961  
North Sydney NSW 2059  
or may be faxed to (02) 9424 5860  
(For advice, telephone the Duty  
Pharmaceutical Officer on 02 9391 9944.)
- count the quantity of drugs of addiction held and enter the particulars in a new register.

If the medical practitioner loses (or has stolen from them) a drug of addiction, they must immediately notify Pharmaceutical Services by completing the online ‘Notification of Loss or Theft of Accountable Drugs (S8 and S4D substances)’ located on the Internet at: <http://www.health.nsw.gov.au/pharmaceutical/Pages/lost-stolen-drugs.aspx> and enter the relevant details in the drug register. The police should also be notified where theft has occurred.

#### d. Authority to prescribe and administer buprenorphine injections

All patients commencing treatment with depot BPN must be enrolled on the NSW Opioid Treatment Program. Authorisation to prescribe BPN must be granted by the Ministry of Health under the provisions of Section 29 of the Poisons and Therapeutic Goods Act before commencing the treatment.

The medical practitioner must make a record in the patient’s file kept at the surgery, clinic or hospital, each time the medical practitioner prescribes and administer the buprenorphine depot injections. The record in the patient’s file should have the following particulars:

- patient’s name and address
- date of prescribing and date of administration
- the drug name (including the brand name), strength and the interval in which the injections are to be administered.

The medical practitioner must also record the particulars of administration in the drug register (as noted above).



# 12.

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# 13.

## Appendix

### a) Drug drug interactions (DDIs)

Drug-drug interactions of potential clinical relevance with depot BPN

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Benzodiazepines and Other Central Nervous System (CNS) Depressants	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, and other opioids	<ul style="list-style-type: none"> <li>- Increases the risk of respiratory depression, profound sedation, coma, and death</li> <li>- Use of these substances should be avoided or minimised during treatment with buprenorphine formulations. Patients should be advised of the extreme danger of concomitant use of sedatives while receiving depot BPN treatment</li> </ul>
CYP3A4 inhibitors	Macrolide antibiotics azole-antifungal agents protease inhibitors (e.g. erythromycin, ketoconazole, ritonavir, nelfinavir, indinavir, intraconazole)	<ul style="list-style-type: none"> <li>- An interaction study of buprenorphine with ketoconazole resulted in increased C<sub>max</sub> (approximately 50%) and AUC (approximately 70%) of buprenorphine and, to a lesser extent, of the metabolite, norbuprenorphine</li> <li>- Patients receiving buprenorphine should be closely monitored for signs and symptoms of buprenorphine toxicity and may require dose reduction if combined with potent CYP3A4 inhibitors. The dose of either buprenorphine or the CYP3A4 inhibitor may need to be adjusted accordingly In practice, doses rarely need to be adjusted</li> <li>- Monitor for buprenorphine withdrawal if the concomitant medication is discontinued after the patient is stable on depot BPN</li> </ul>
CYP3A4 Inducers	Rifampin Carbamazepine Phenytoin Phenobarbital	<ul style="list-style-type: none"> <li>- Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence. It is recommended that patients receiving buprenorphine should be closely monitored if inducers are co-administered. The dose of either buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly In practice, doses rarely need to be adjusted</li> <li>- Monitor for signs and symptoms of buprenorphine toxicity or overdose, if the CYP3A4 inducers is discontinued after the patient is stable on depot BPN</li> </ul>
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz Nevirapine Etravirine Delavirdine	<ul style="list-style-type: none"> <li>- Significant pharmacokinetic interactions between NNRTIs and sublingual buprenorphine have been shown, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects</li> <li>- Monitor for increase or decrease in therapeutic effects of NNRTIs</li> </ul>

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Antiretrovirals: Protease inhibitors (PIs)	Atazanavir Ritonavir	<ul style="list-style-type: none"> <li>- Treatment with atazanavir or atazanavir/ritonavir may result in elevated levels of buprenorphine</li> <li>- If atazanavir +/- ritonavir is initiated once the patient is stable on depot BPN, monitor for signs and symptoms of over-medication with buprenorphine. If necessary, reduce depot BPN dose from 300 to 100mg, or discontinue depot BPN and treat with sublingual buprenorphine to enable rapid dose adjustments</li> </ul>
Drugs that affect the serotonin neurotransmitter system	Selective serotonin reuptake inhibitors (SSRIs) Serotonin and norepinephrine reuptake inhibitors (SNRIs) Trazodone, Tramadol Linezolid and intravenous methylene blue Tricyclic antidepressants (TCAs)	<ul style="list-style-type: none"> <li>• May result in serotonin syndrome in high doses (e.g. overdose). Monitor for signs and symptoms of serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug</li> </ul>
Monoamine Oxidase Inhibitors (MAOIs)	e.g. Phenelzine, tranylcypromine, linezolid	<ul style="list-style-type: none"> <li>• MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma)</li> <li>• It is recommended that patients receiving buprenorphine and MAOI should be closely monitored</li> <li>• Exacerbation of the opioid effects based on experience with morphine</li> </ul>
Diuretics		<ul style="list-style-type: none"> <li>- May reduce the efficacy of diuretics by inducing the release of antidiuretic hormone</li> <li>- Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed</li> </ul>
Anticholinergic Drugs		<ul style="list-style-type: none"> <li>- May increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus</li> <li>- Monitor for signs of urinary retention or reduced gastric motility</li> </ul>
Opioid antagonists	Naltrexone Naloxone Nalmefene	<ul style="list-style-type: none"> <li>- Opioid antagonists should generally not be used outside of emergency situations in patients in opioid agonist treatment, including depot BPN.</li> <li>- Naloxone may be administered in response to an opioid overdose, multiple injections or an infusion of naloxone may be required.</li> <li>- For opioid-dependent patients currently receiving buprenorphine treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone</li> </ul>

Drug Class	Drug(s) within Class	Clinical effect and suggested management
Opioid analgesics	Opioids	<ul style="list-style-type: none"> <li>- Buprenorphine may reduce the effects of opioid analgesics through receptor blockade. Patients requiring analgesia should include non-opioid approaches (e.g. NSAIDs, ketamine). Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration, requiring close monitoring of opioid effects</li> <li>- Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. The potential for overdose also exists with a full agonist, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining</li> </ul>
Gabapentinoids	Gabapentin, pregabalin, baclofen	<ul style="list-style-type: none"> <li>- This combination may result in death due to respiratory depression. Therefore, dosages must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be cautioned to use gabapentinoids concurrently with this product only as directed by their physician</li> </ul>
Alcohol	Alcoholic drinks or medications containing alcohol	<ul style="list-style-type: none"> <li>- Alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of buprenorphine</li> </ul>

## b) Depot BPN studies

c) Study Reference	Product	Setting	Author
NCT02672111 HS-14-499 (Braeburn)	Buvidal®	Community AUS	Frost et al 2019

**Aims:** To assess long-term safety of subcutaneous buprenorphine depot (CAM2038) weekly and monthly regimens in adult outpatients with opioid use disorder.

**Methods:** This phase 3, open-label, multicentre, 48-week study (ClinicalTrials.gov NCT02672111) was conducted at 26 sites (US, UK, Hungary, Denmark, Sweden, Germany, and Australia). Participants were administered CAM2038 weekly (8, 16, 24, or 32mg) or CAM2038 monthly (64, 96, 128, or 160mg) with flexible dosing and individualised titration up or down utilising the multiple CAM2038 weekly and monthly dosing options. Safety variables, urine toxicology samples, and self-reported illicit opioid use were collected at each visit. 162/227 (71.4%) participants were administered a patient satisfaction survey.

**Results:** Between December 14, 2015, and April 12, 2017, 228 opioid-dependent participants enrolled, and 227 participants received CAM2038 (37 initiated directly onto CAM2038 and 190 converted from sublingual buprenorphine). 167/227 (73.6%) participants completed the treatment period. 143/227 (63.0%) participants reported at least 1 treatment emergent adverse event (TEAE), and 60/227 (26.4%) reported a drug-related TEAE. 46/227 (20.3%) participants reported injection site reactions, with most (45/46 [97.8%]) reported as mild to moderate. 128/227 (56.4%) of the TEAEs were mild or moderate in severity. Five participants (2.2%) discontinued study drug due to a TEAE, of which 2 cases (0.9%) were injection site related. No serious AEs were attributed to study drug. At end of study, the percentage of the composite outcome comprising illicit opioid-negative urine samples and self-reports was 63.0% (17/37) in new-to-treatment participants and 82.8% (111/190) for participants converted from sublingual buprenorphine. Participants reported high levels of satisfaction with CAM2038.

**Conclusions:** CAM2038 was well-tolerated and demonstrated a systemic safety profile consistent with the known profile of sublingual buprenorphine. Weekly and monthly CAM2038 was associated with high retention rates and low levels of continued illicit opioid use throughout the study (12)

Study Reference	Product	Setting	Author
NCT02611752	Buvidal®	US	Walsh et al 2017

**Importance:** Buprenorphine is an efficacious, widely used treatment for opioid use disorder (OUD). Daily oral transmucosal formulations can be associated with misuse, diversion, and nonadherence; these limitations may be obviated by a sustained release formulation.

**Objective:** To evaluate the ability of a novel, weekly, subcutaneous buprenorphine depot formulation, CAM2038, to block euphorogenic opioid effects and suppress opioid withdrawal in non-treatment-seeking individuals with OUD.

**Design, Setting and Participants:** This multisite, double-blind, randomized within-patient study was conducted at 3 controlled inpatient research facilities. It involved 47 adults with DSM-V moderate-to-severe OUD. The study was conducted from October 12, 2015 (first patient enrolled), to April 21, 2016 (last patient visit).

**Interventions:** A total of five 3-day test sessions evaluated the response to hydromorphone (0, 6, and 18mg intramuscular in random order; 1 dose/session/day). After the first 3-day session (ie, qualification phase), participants were randomized to either CAM2038 weekly at 24mg (n = 22) or 32mg (n = 25); the assigned CAM2038 dose was given twice, 1 week apart (day 0 and 7). Four sets of sessions were conducted after randomization (days 1-3, 4-6, 8-10, and 11-13). Weekly CAM2038 doses were initiated directly from adults maintained on oral morphine.

**Main Outcomes and Measures:** The primary end point was maximum rating on the visual analog scale for drug liking. Secondary end points included other visual analog scale (eg, high and desire to use), opioid withdrawal scales, and physiological and pharmacokinetic outcomes.

**Results:** A total of 46 of 47 randomized participants (mean [SD] age, 35.5 [9] years; 76% male [n = 35]) completed the study. Both weekly CAM2038 doses produced immediate and sustained blockade of hydromorphone effects (liking maximum effect, CAM2038, 24mg: effect size, 0.813; P < .001, and CAM2038, 32mg: effect size, 0.753; P < .001) and suppression of withdrawal (Clinical Opiate Withdrawal Scale, CAM2038, 24mg: effect size, 0.617; P < .001, and CAM2038, 32mg: effect size, 0.751; P < .001). CAM2038 produces a rapid initial rise of buprenorphine in plasma with maximum concentration around 24 hours, with an apparent half-life of 4 to 5 days and approximately 50% accumulation of trough concentration from first to second dose (trough concentration = 0.822 and 1.23 ng/mL for weeks 1 and 2, respectively, with 24mg; trough concentration = 0.993 and 1.47 ng/mL for weeks 1 and 2, respectively, with 32mg).

**Conclusions and Relevance:** CAM2038 weekly, 24 and 32mg, was safely tolerated and produced immediate and sustained opioid blockade and withdrawal suppression without any evidence of precipitating withdrawal upon depot initiation. The results support the use of this depot formulation for treatment initiation and stabilization of patients with OUD, with the further benefit of obviating the risk for misuse and diversion of daily buprenorphine while retaining its therapeutic benefits. (35)

EudraCT # 2008-006348-20	Buvidal®	Hamburg, Germany	Hassen et al 2017
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**Introduction:** Sublingual buprenorphine is effective for opioid dependence treatment but associated with misuse, abuse, and diversion. The present Phase I/II study evaluated a novel buprenorphine subcutaneous depot formulation for once-weekly dosing (CAM2038 q1w) in patients receiving maintenance treatment for opioid use disorder with daily sublingual buprenorphine.

**Methods:** After discontinuation of buprenorphine for 48 h, patients received a single CAM2038 q1w dose based on their pre-study daily sublingual maintenance dose. CAM2038 q1w doses of 7.5, 15, 22.5, and 30mg were administered in a sequential dose-escalating design. The following assessments were performed: pharmacokinetics of buprenorphine and norbuprenorphine, pharmacodynamics (evaluated using the Subjective and Clinical Opiate Withdrawal Scales), and time to intake of rescue sublingual buprenorphine medication.

**Results:** Single doses of CAM2038 q1w indicated dose-proportional buprenorphine pharmacokinetics (C<sub>max</sub> and AUC<sub>0-7d</sub>), with time to C<sub>max</sub> ~20 h and an apparent terminal half-life of 3-5 days, supporting once-weekly dosing. On average, patients showed a rapid and extended decrease in opiate-withdrawal symptoms from baseline, with zero or very low SOWS and COWS values measured at least up to 7 days after dosing of CAM2038 q1w. The median time to first use of rescue buprenorphine was 10 days. No dose dependence was seen in the pharmacodynamics, attributable to the selection of CAM2038 q1w doses based on patients' pre-study maintenance doses. CAM2038 q1w was safe and generally well tolerated.

**Conclusions:** Pharmacokinetics and pharmacodynamics of a novel buprenorphine subcutaneous depot formulation for once-weekly dosing was evaluated, suggesting utility in maintenance treatment of patients with opioid use disorder. (36)

Study Reference	Product	Setting	Author
	Buvidal®	US	Liu et al 2018
<p>CAM2038, FluidCrystal injection depot, is an extended release formulation of buprenorphine given subcutaneously every 1 week (Q1W) or every 4 weeks (Q4W). The purpose of this research was to predict the magnitude of drug-drug interaction (DDI) after coadministration of a strong CYP3A4 inducer or inhibitor using physiologically based pharmacokinetic (PBPK) modelling.</p> <p>A PBPK model was developed for CAM2038 based on the previously published buprenorphine PBPK model after intravenous and sublingual administration and the PK profiles after subcutaneous administration of CAM2038 from 2 phase I clinical trials. The strong CYP3A4 inhibitor ketoconazole was predicted to increase the buprenorphine exposure by 35% for the Q1W formulation and 34% for Q4W formulation, respectively. Also, the strong CYP3A4 inducer rifampin was predicted to decrease the buprenorphine exposure by 26% for both the Q1W and Q4W formulations.</p> <p>The results provided insight into the potential DDI effect for CAM2038 and suggested a lack of clinically meaningful DDI when CAM2038 is coadministered with CYP3A4 inhibitor or inducer. Therefore, no dose adjustment is required when CAM2038 is coadministered with CYP3A4 perpetrators (37)</p>			
NCT02357901	Sublocade®	Community US	Haight et al 2019
<p><b>Background:</b> BBP-6000, referred to as BUP-XR (extended-release buprenorphine), is a subcutaneously injected, monthly buprenorphine treatment for opioid use disorder. BUP-XR provides sustained buprenorphine plasma concentrations to block drug-liking of abused opioids over the entire monthly dosing period, while controlling withdrawal and craving symptoms. Administration of BUP-XR in a health-care setting also mitigates abuse, misuse, diversion, and unintentional exposure. We aimed to investigate the efficacy of different BUP-XR dosing regimens in participants with opioid use disorder.</p> <p><b>Methods:</b> This randomised, double-blind, placebo-controlled, phase 3 trial was done at 36 treatment centres in the USA. Treatment-seeking adults aged 18–65 years who had moderate or severe opioid use disorder (as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders) entered an open-label run-in phase of up to 2 weeks' treatment with buprenorphine-naloxone sublingual film. Eligible participants were then randomly assigned (4:4:1:1) with an interactive voice/web-response system to receive BUP-XR 300 mg/300 mg (six injections of 300 mg), BUP-XR 300 mg/100 mg (two injections of 300 mg plus four injections of 100 mg), or volume-matched placebo every 28 days, and received weekly individual drug counselling. No supplemental buprenorphine was allowed. The primary efficacy endpoint was participants' percentage abstinence from opioid use, defined as the percentage of each participant's negative urine samples and self-reports of illicit opioid use from week 5 to week 24, analysed in the full analysis set. Safety was assessed in all participants who received at least one dose of BUP-XR or placebo. This study is registered with ClinicalTrials.gov, number NCT02357901.</p> <p><b>Findings:</b> From Jan 28, 2015, to Nov 12, 2015, 1187 potential participants were screened, 665 entered run-in, and 504 received BUP-XR 300 mg/300 mg (n=201), BUP-XR 300 mg/100 mg (n=203), or placebo (n=100). Mean participants' percentage abstinence was 41.3% (SD 39.7) for BUP-XR 300 mg/300 mg and 42.7% (38.5) for 300 mg/100 mg, compared with 5.0% (17.0) for placebo (<math>p &lt; 0.0001</math> for both BUP-XR regimens). No compensatory non-opioid drug use was observed during BUP-XR treatment. The most common adverse events were headache (17 [8%] participants in the BUP-XR 300 mg/300 mg group vs 19 [9%] participants in the BUP-XR 300 mg/100 mg group vs six [6%] participants in the placebo group), constipation (16 [8%] vs 19 [9%] vs 0), nausea (16 [8%] vs 18 [9%] vs five [5%]), and injection-site pruritis (19 [9%] vs 13 [6%] vs four [4%]). The BUP-XR safety profile was consistent with other buprenorphine products for treatment of opioid use disorder, except for injection-site reactions, which were reported in more than 5% of all participants who received BUP-XR, but were mostly mild and not treatment-limiting.</p> <p><b>Interpretation:</b> Participants' percentage abstinence was significantly higher in both BUP-XR groups than in the placebo group. Treatment with BUP-XR was also well tolerated. The availability of this monthly formulation, delivered by health-care providers, represents an advance in treatment for opioid use disorder that enhances the benefits of buprenorphine by delivering sustained, optimal exposure, while reducing risks of current buprenorphine products (8)</p>			

Study Reference	Product	Setting	Author
NCT02044094	Sublocade®	Community US	Indivior 2002

**Background:** Buprenorphine's two key effects of reducing craving and attenuating the response to opioid drugs contribute to reduce the self-administration of opioids. In the development of Buprenorphine as a monthly, sustained-release formulation (Sublocade®) achieving plasma levels to demonstrate attenuation of opioid effects is an important dose confirmation step.

**Objective:** The objective of this study was to demonstrate that Sublocade® blocks the subjective effects and reinforcing efficacy of the  $\mu$ -opioid receptor agonist hydromorphone (intramuscularly administered) in subjects with moderate or severe opioid use disorder.

**Methods:** Subjects were first inducted and dose stabilized on sublingual buprenorphine/naloxone (8–24 mg daily; dose expressed as the buprenorphine component), then received two subcutaneous injections of RBP-6000 (300 mg) on Day 1 and Day 29. Hydromorphone (HM) challenges (6 mg, 18 mg or placebo administered in randomized order) occurred on 3 consecutive days of each study week before and after receiving RBP-6000. Subjects reported their responses to each challenge on various 100-mm Visual Analogue Scales (VAS). Subjects also completed a choice task to assess the reinforcing efficacy of each hydromorphone dose relative to money. The noninferiority (NI) margin, the largest difference allowed for the 6 or 18 mg HM VAS to exceed the placebo VAS (the maximum VAS recorded following IM injection of 0 mg HM) before being considered significant, was set at 20. Based on comparison to the historical response to opioid agonists in unblocked subjects, a difference of less than 20 points (on a unipolar scale) between the mean maximum response to hydromorphone and the mean maximum placebo response for the same challenge was considered to indicate near-complete blockade.

**Results:** All 12 weeks of the treatment period demonstrated blockade for both 6 mg and 18 mg following Sublocade® injections. However, wide variation can be seen in isolated measurements from individual subjects, shown in the figure below. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade® injection. For comparison, stabilization doses of SL buprenorphine in Week 0 failed to provide full blockade to 18 mg of HM.

**Conclusion:** This study demonstrated that RBP-6000 at a 300 mg dose provides durable and potent blockade of the subjective effects and reinforcing efficacy of hydromorphone in subjects with moderate or severe opioid use disorder. (34)

Summary based on US prescribing information.

NCT02651584	Buvidal®	Community US	Lofwall et al 2018
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**Objective** To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is non-inferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

**Design, Setting and Participants** This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

**Interventions** Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

**Main Outcomes and Measures** Primary end points tested for non-inferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 pre-specified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21–24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4–24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated non-inferiority.

**Results** A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95%CI, -4.0% to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95%CI, -0.1% to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

**Conclusions and Relevance** Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages. (4)



Study Reference	Product	Setting	Author
ISRCTN24987553 HS-13-438	Buvidal®	Community	Albayaty et al 2017

**Introduction** CAM2038 q1w (once weekly) and q4w (once monthly) are investigational buprenorphine subcutaneous (SC) formulations based on FluidCrystal® injection depot technology. These two drug products are being developed for opioid dependence treatment, with a target for once-weekly and once-monthly SC dosing. The rationale for developing two products with different dosing frequencies is that treatment strategies/routines, and hence different treatment preferences, can vary between patients, different stages of opioid maintenance treatment, and countries. This study evaluated the pharmacokinetics and safety of buprenorphine and norbuprenorphine following administration of CAM2038 q1w or q4w versus active controls.

**Methods** Healthy volunteers were randomized to five treatment groups. All received a single intravenous dose of buprenorphine 600 µg, followed post-washout by a single dose of CAM2038 q4w 96mg, a single dose of CAM2038 q4w 192mg, or sublingual buprenorphine 8, 16, or 24mg daily for 7 days, followed post-washout by a single dose of CAM2038 q4w 64 or 128mg or four repeated weekly doses of CAM2038 q1w 16mg. All subjects received daily naltrexone.

**Results** Eighty-seven subjects were randomized. Median buprenorphine t<sub>max</sub> after CAM2038 q4w was 4–10 h (24 h for CAM2038 q1w); mean terminal half-life was 19–25 days (5 days for CAM2038 q1w). CAM2038 q4w showed dose-proportional buprenorphine release, with similar exposure to repeat-dose CAM2038 q1w at comparable monthly dose level. Both CAM2038 formulations showed complete absolute bioavailability of buprenorphine and 5.7- to 7.7-fold greater buprenorphine bioavailability versus sublingual buprenorphine. CAM2038 q1w and q4w were well tolerated; subjects' acceptance was higher for CAM2038 than for sublingual buprenorphine 1 h post-dose.

**Conclusions** The pharmacokinetic profiles of CAM2038 q1w and q4w versus sublingual buprenorphine support expected treatment efficacy with once-weekly and once-monthly dosing, respectively. CAM2038 formulations were safe and showed good local tolerability (38)

### c) Pregnancy statement – checklist

#### Pregnancy Statement – Checklist of issues to be discussed with pregnant patients Patient Consent Form

Key issues to be considered in managing pregnant women who are already being managed with Buvidal® Weekly, Buvidal® Monthly or Sublocade® are:

- patients should be involved in decision making regarding their treatment
- opiate agonist treatment is first line treatment for opiate dependence during pregnancy
- optimal ante-natal care for pregnant women who are on opiate agonist treatment includes regular liaison between their opiate treatment team and ante-natal team

Pregnant women may choose to continue treatment with Buvidal® Weekly, Buvidal® Monthly or Sublocade® during pregnancy and breastfeeding if the benefits outweigh the risks to the pregnant woman and her baby.

If this does occur, in the patients' clinical file the following points should be adequately documented.

- the safety of depot buprenorphine during pregnancy and breastfeeding has not yet been established
- pregnancy and breastfeeding are currently listed as contraindications for the use of Buvidal® Weekly and Monthly in Australia by the Therapeutic Goods Administration
- the patient has been involved in a discussion regarding their treatment decision including risks and benefits and has agreed to continue depot buprenorphine treatment

### e) Buvidal® Weekly product information AUS

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02610-1>

### d) Buvidal® Monthly product information AUS

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02611-1>

### f) Sublocade® product information AUS

<https://www.ebs.tga.gov.au/>

### g) Sublocade® prescribing information US

<https://www.sublocade.com/Content/pdf/prescribing-information.pdf>







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