Long-Acting Injection Buprenorphine in the Treatment of Opioid Dependence

Queensland Clinical Guidelines: 2019
Long-acting injection buprenorphine in the treatment of opioid dependence – Queensland Clinical Guidelines 2019

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Summary

These guidelines align with the latest clinical evidence for treatment of opioid dependence, however they cannot provide detailed direction for managing every client in every situation. In some circumstances, clinicians may need to vary their clinical practices from these guidelines. It is essential that, under such circumstances, clinicians clearly document the reasons for not following the guidelines in the clinical record. Individual medical practitioners, nurse practitioners, pharmacists and other clinical staff are responsible for decisions about the safety and effectiveness of treatment for each client. These guidelines are not intended to replace professional judgement in individual cases.

Individual services should develop workplace instructions and procedures that remain consistent with both the national and state guidelines while reflecting local needs and circumstances.

In this document, ‘Medication-Assisted Treatment of Opioid Dependence’ (MATOD) refers specifically to treatment of opioid dependence using opioid agonists and opioid partial agonists.

The term ‘client’ is used to refer to people seeking assistance with opioid dependence from MATOD service providers. The terms patient, service user, consumer, person who uses drugs or person who injects drugs are used in various other settings.

For the purpose of this document, buprenorphine refers to both buprenorphine-mono (Subutex®), buprenorphine/naloxone (Suboxone®) and long-acting injection buprenorphine unless specifically stated.

All treatment and care are provided with due consideration for the client’s human rights.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCAS</td>
<td>Alcohol and Drug Clinical Advisory Service</td>
</tr>
<tr>
<td>BPN</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>COWS</td>
<td>Clinical Opiate Withdrawal Scale</td>
</tr>
<tr>
<td>CS</td>
<td>Consensus Statement</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-Drug Interaction</td>
</tr>
<tr>
<td>FC</td>
<td>FluidCrystal®</td>
</tr>
<tr>
<td>HDPR</td>
<td>Health (Drugs and Poisons) Regulation 1996</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine Growth Restriction</td>
</tr>
<tr>
<td>LAI</td>
<td>Long-acting Injection</td>
</tr>
<tr>
<td>LAI BPN</td>
<td>Long-acting Injection Buprenorphine</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Monoamine Oxidase Inhibitors</td>
</tr>
<tr>
<td>MATOD</td>
<td>Medication-Assisted Treatment of Opioid Dependence</td>
</tr>
<tr>
<td>NAS</td>
<td>Neonatal Abstinence Syndrome</td>
</tr>
<tr>
<td>NMP</td>
<td>N methyl 2 pyrrolidone</td>
</tr>
<tr>
<td>NOWS</td>
<td>Neonatal Opioid Withdrawal Syndrome</td>
</tr>
<tr>
<td>NTX</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
</tr>
<tr>
<td>SL BPN</td>
<td>Sublingual Buprenorphine</td>
</tr>
<tr>
<td>SL BPN NX</td>
<td>Sublingual Buprenorphine / Naloxone</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
</tbody>
</table>
### Table 1: Overview of buprenorphine products available for treatment of opioid dependence in Australia

<table>
<thead>
<tr>
<th>Formulations</th>
<th>SL Suboxone® and Subutex®</th>
<th>Buvidal® Weekly and Monthly</th>
<th>Sublocade®</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL Suboxone® contains buprenorphine (BPN) and naloxone in 4:1 ratio 2/0.5mg and 8/2mg sublingual film</td>
<td>Buvidal® Weekly and Monthly contain BPN in FluidCrystal® LAI 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 Buvidal® Monthly: 64mg/0.18 mL; 96mg/0.27 mL; 128mg/0.36 mL</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Subutex® contains buprenorphine in 0.4mg, 2mg and 8mg sublingual tablets.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Storage Requirements | Store at room temperature (below 25°C). Store in accordance with the Queensland legislation relating to scheduled medicines. | Store at room temperature (below 25°C). Do not refrigerate or freeze. Store in accordance with the Queensland legislation relating to scheduled medicines. | 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. Store in accordance with the Queensland legislation relating to scheduled medicines. |

| 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 (tmax) Buvidal® Weekly = 24hrs Buvidal® Monthly = 6-10hrs Half life Buvidal® Weekly = 3-5 days Buvidal® Monthly = 19-25 days | Bioavailability = 100%. Time to peak plasma levels ((tmax) = 24hrs. Half life = 43 to 60 days. Steady-state equilibrium by 2nd (300/100mg) to 6th dose (300/300mg). |

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### Frequency of dosing

<table>
<thead>
<tr>
<th>Steady-state equilibrium by 4th dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buvidal® Weekly dose can be administered every 7±2 days (5-9 day schedule).</td>
</tr>
<tr>
<td>Buvidal® Monthly dose can be administered every 4±1 weeks (3-5 week schedule).</td>
</tr>
<tr>
<td>Sublocade® dosed every 4 weeks (26-42 day schedule).</td>
</tr>
</tbody>
</table>

#### 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 these 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 very rare (e.g. serotonin toxicity in combination with medication such as SSRIs, MAOIs, tramadol; or medications that can cause QT prolongation and increase risk of cardiac arrhythmias).

Long duration of effects of LAI 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 LAI.

### Recommended dosing regimen

<table>
<thead>
<tr>
<th>From heroin, pharmaceutical opioids:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commence 8mg Day 1 when client in early / mild opioid withdrawal (usually &gt;8-12hrs after last dose or use).</td>
</tr>
<tr>
<td>Titrate upwards on daily basis as required.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From methadone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate BPN when client in moderately severe withdrawal (e.g. COWS≥12) (e.g.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buvidal® dose should be determined according to client’s SL BPN dose (see Table 5).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titrate subsequent doses after clinical review.</td>
</tr>
<tr>
<td>Note increasing effects during first few doses (accumulation to steady state after about 4 doses).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initiate treatment with SL BPN (at least 8mg) for ≥7 days, then transfer to Sublocade®.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended induction:</td>
</tr>
<tr>
<td>300mg monthly injections x 2 doses (8 weeks).</td>
</tr>
<tr>
<td>then 100mg monthly doses (if client ‘stable’ on initial 2 x 300mg doses) or 300mg monthly doses if require additional BPN effects (e.g. cravings, withdrawal, continued opioid use).</td>
</tr>
</tbody>
</table>
### Maintenance phase

<table>
<thead>
<tr>
<th>Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjust dose to achieve treatment goals (reduced use of other opioids, reduced withdrawal and cravings; blockade effects). Range 2-32mg daily; most clients require 12-24mg daily.</td>
<td>Titrate dose to achieve treatment goals. Adjust doses when transferring between weekly and monthly doses.</td>
</tr>
<tr>
<td>Key adverse events</td>
<td>Systemic BPN adverse events</td>
</tr>
</tbody>
</table>

### Withdrawal phase

<table>
<thead>
<tr>
<th>Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradually taper dose over several weeks-months (e.g. 2-4mg weekly reductions).</td>
<td>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).</td>
</tr>
<tr>
<td>Key adverse events</td>
<td>Systemic BPN adverse events. Local injection site:</td>
</tr>
<tr>
<td></td>
<td>• Redness, pain, tenderness, swelling in approximately 5-10% clients.</td>
</tr>
<tr>
<td></td>
<td>• Usually mild and transient and resolves spontaneously.</td>
</tr>
</tbody>
</table>

### Initiation

Clients may be initiated with 100mg Sublocade® (after ≥7 days SL BPN treatment) doses if:

- safety concerns (e.g. severe hepatic disease).
- DDI concerns: e.g. overdose risk from polysubstance use.

There is no published safety data for initiating Sublocade® in clients on low dose SL BPN (<8mg).

### Key adverse events

- Systemic BPN adverse events
- Local injection site:
  - Redness, pain, tenderness, swelling in approximately 5-10% clients.
  - Usually mild and transient and resolves spontaneously.

---

Long-Acting Injection Buprenorphine in the Treatment of Opioid Dependence – Queensland Clinical Guidelines 2019

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Background

This clinical guideline has been developed to inform decision-making by clinicians and clients prescribing and/or being treated with the following long-acting injection buprenorphine (LAI 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) is approved for use in the US, and available as an investigational product in Australia. It was registered by the TGA in Australia in August 2019 for ‘maintenance treatment of opioid dependence within a framework of medical, social and psychological support’.

At the time of writing, Buvidal® weekly and Buvidal® monthly preparations were granted Pharmaceutical Benefits Scheme (PBS) listing as a schedule 100 drug on 1st September 2019, and Sublocade® products are awaiting decisions regarding PBS listing.

This guideline has been developed for treatment using LAI 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 Hospital and Health Services (including correctional facilities);
- Private opioid treatment prescribers;
- Community settings with health professionals experienced in the use of buprenorphine where a member of the treatment team holds an approval to prescribe buprenorphine for clients for the treatment of opioid dependence.

This guideline is to be used in conjunction with the Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018 (1) and the National Guidelines for Medication-Assisted Treatment of Opioid Dependence 2014 (2). State and National guidelines will be revised in the future to incorporate LAI 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 Buvidal® 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 registered 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 QLD (1);
- Clinical experience in using LAI BPN products in Australian clinical trials (See 13.2 - LAI BPN Studies);
• Consensus expert opinion of clinicians and consumer representatives including the guideline working group formed by the NSW Ministry of Health and clinicians / consumers involved in pre-registration clinical trials of these products.

This Queensland clinical guideline was adapted from the NSW Clinical Guideline: Use of depot BPN in the treatment of opioid dependence. This guideline aims to provide a framework for clinical decision making by clinicians and consumers across a range of service settings involved in the delivery of treatment with LAI BPN products.

As clinical experience with LAI 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 is intended to be reviewed in 12 months following release.
1. **Introduction to MATOD with LAI BPN medications**

1.1 **Overview of treatment model of care**

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

(a) safe and effective use of medicine;
(b) regular clinical reviews and monitoring;
(c) availability of psychosocial interventions; and
(d) addressing medical, mental health and social comorbidities.

Australia has previously been restricted to medications designed to be administered once a day (or at up to three-day intervals for a small proportion of clients treated with SL BPN). The risks associated with methadone and buprenorphine (diversion to others, injecting medications, overdose risks, particularly 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 clients and service providers and has been cited as a barrier to engagement and retention of some clients in treatment.

The introduction of LAI BPN formulations into the Australian treatment system represents a significant development in this model of care. The availability of LAI BPN may have several potential benefits:

- **Greater convenience for clients in that they will not have to attend dosing sites (pharmacies, clinics) on a frequent basis for supervised dosing.** In Australia, most clients in SL BPN treatment attend daily or several times a week for supervised dosing. This raises difficulties in regional and rural settings, where clients often have to travel large distances to reach dosing sites. This will also benefit clients for whom regular attendance at pharmacies is difficult (e.g. due to mobility problems, work issues, carer responsibilities), 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 clients and service providers.** The Australian treatment system predominantly involves supervised dosing (with some ‘take-away’ doses) at community pharmacies for which most clients pay between $35 to $50 per week. This cost is a significant burden for many clients - 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 client. In the public system, significant staffing resources are involved in supervised dosing and liaising with pharmacies about unsupervised dosing (TADs) rather than case management or providing health-related and/or psychosocial interventions, and it is envisaged that treatment with LAI 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 clients engage in non-
medical use of buprenorphine (injecting, diversion to others, stockpiling) (6). This is of particular concern in correctional settings, and has restricted the use of buprenorphine in those settings across Australia.

- Greater medication adherence and enhanced treatment outcomes for some clients who struggle to attend regularly for dosing with SL BPN. Some clients with opioid dependence struggle to attend regularly for dosing with SL BPN due to homelessness, cognitive impairment, domestic violence, child-care responsibilities, psychiatric co-morbidity, physical mobility problems (particularly with an ageing treatment population), or regular episodes of incarceration (e.g. watch house). Often these clients are also not suitable for large numbers of take-away doses of buprenorphine, and therefore find themselves in a cycle of missed doses, polydrug use, and deteriorating health and social conditions. Such clients may benefit from less frequent (e.g. weekly or monthly) dosing requirements with the LAI product, yet maintain buprenorphine adherence and experience greater ‘stability’.

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

1.2 Evidence of efficacy of LAI 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 13.2 - LAI 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 on individuals are dose-dependent within a limited range, above which increasing doses does not produce corresponding increases in effect. Thus, for certain opioid 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 antagonism 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 LAI 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).

2.1 Formulations

2.1.1 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® LAI contains the active substance BPN in delivery system compositions based on the proprietary FluidCrystal® LAI technology - a lipid-based liquid. When injected SC 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 encapsulates the active substance. This results in a slow and consistent release of BPN over a week or a month depending on the composition. Excipients are described in the Product Label (see sections 13.4 and 13.5).

2.1.2 Sublocade® formulations

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

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 needle.

2.2 Overview of pharmacokinetic properties

The key pharmacokinetic properties of Buvidal® and Sublocade® are detailed in the Product Labels (see sections 13.4, 13.5 and 13.6) and summarised in this section for comparison between the two products.
It is important to recognise that repeated use of the LAI BPN formulations results in accumulation over time, and steady state equilibrium in achieved after approximately three to six weekly/monthly doses. The average (Cavg), peak (Cmax) and trough (Cmin) BPN plasma concentrations seen at steady state (after four doses) of the various LAI 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 ≥ 50% μ opioid receptor occupancy (μORO), which is often associated with BPN plasma concentrations ≥ 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. ≥ 70-80%) μORO, which is commonly associated with higher BPN plasma concentrations (e.g. ≥ 2-3 ng/mL (10,11)). These plasma levels are generally achieved by all LAI BPN formulations. Whilst laboratory receptor-binding studies are of interest in understanding this treatment approach, they do not translate into clinical practice readily, and there is no clinical role for monitoring BPN plasma levels as part of client care. At this time, routine measures of BPN plasma levels are not available nor can opioid receptor occupancy be assessed in clinical practice: few laboratories have the capacity to accurately quantify buprenorphine and norbuprenorphine levels, tests are not reimbursed by Medicare, requiring the client or clinician to pay for the tests, and findings are very difficult to interpret. Rather clinicians should focus upon individual client responses to treatment, with reviews of client 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.

However, it should be emphasised that plasma BPN levels only partially account for the clinical effects experienced by clients – 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 client expectation, concomitant medical (e.g., chronic pain, hepatic disease) and psychiatric conditions, use of opioids and other substances, drug-drug interactions, adverse events and genetic variation in BPN metabolism. Whilst expected plasma concentrations routinely achieved with formulations can serve as a guide to the choice of BPN doses and formulation, clinical titration, with regular client monitoring is required.
2.2.1 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.
2.2.2 Metabolism
The metabolism of BPN is unaffected by the formulation. Variation in plasma terminal half-life and duration of effect relates to differences in the rate of release of BPN 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 LAI BPN results in significantly lower plasma concentrations of norbuprenorphine metabolite compared to SL BPN, avoiding the first-pass metabolism invariably seen with some swallowing of sublingual doses.

2.2.3 Elimination and duration of effects
The slow release of BPN from the LAI formulations results in extended duration of action of these products. The terminal plasma half-life of single doses of the LAI 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 after 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 6th month of the 300/300 regimen, 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 LAI BPN dosing will depend upon the formulation administered (weekly or monthly), the dose of buprenorphine 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.
Long-Acting Injection Buprenorphine in the Treatment of Opioid Dependence

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(Sublocade® 300mg). The prolonged duration of effects of LAI 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 loss of tolerance to opioids and be protective against overdose following relapse to heroin or other opioid use.

2.2.4 Withdrawal, cravings, opioid blockade

Clinical trials indicate that both Buvidal® (7) and Sublocade® (8) are effective in reducing opioid withdrawal and opioid cravings. Withdrawal after ceasing Buvidal® or Sublocade® is described in 13.2 - LAI 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 due to its greater affinity for mu opioid receptors than many other 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 13.2 - LAI BPN Studies.

2.3 Side effects and safety issues

2.3.1 Adverse events

Side effects of LAI BPN are similar to the known safety profile of BPN administered sublingually (1,2), with the exception of adverse events related to injection of the drug (12). Readers are referred to product labels (see sections 13.4, 13.5 and 13.6) for detailed information.

Table 2 LAI BPN Adverse Events

<table>
<thead>
<tr>
<th>Injection site related adverse events</th>
<th>Buvidal® PI</th>
<th>Sublocade® PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>8.9%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6.1%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Induration</td>
<td>2.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Bruising</td>
<td>1.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Swelling</td>
<td>4.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Erythema</td>
<td>5.6%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic adverse events</th>
<th>Buvidal® PI</th>
<th>Sublocade® PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>7.7%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.5%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

NB: this is not a head to head study – data has been taken from studies with different reporting frameworks (see 13.4 – 13.6 for details in PI)
2.3.2 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 clients 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.

2.4 Special warnings

2.4.1 Risk of serious harm or death with intravenous administration
Care must be taken to avoid inadvertent injection of LAI 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 LAI BPN forms a firm gel upon contact with body fluids. Animal studies suggest that occlusion, local tissue damage, and thromboembolic events, including life threatening pulmonary emboli, may occur if administered intravenously.

2.4.2 Risk of respiratory and central nervous system (CNS) depression
BPN has been associated with life-threatening respiratory depression. Use LAI BPN with caution in clients 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 LAI BPN is discontinued as a result of compromised respiratory function, monitor clients for ongoing BPN effects for several months.

2.4.3 Precipitation of opioid withdrawal in clients 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 LAI BPN especially for clients on long acting opioids e.g. methadone. Verify that clients have tolerated and are stabilised on daily SL BPN for at least 7-days before commencing treatment with LAI BPN.

2.4.4 Managing risks from concomitant use of benzodiazepines or other CNS depressants
LAI BPN provides higher average blood levels 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 LAI 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 client’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.

2.4.5 Hepatitis, hepatic events and liver disease

Child Pugh class B or C cirrhosis 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 LAI BPN has not been studied. Due to the long-acting nature of the product, adjustments to LAI BPN doses are not rapidly reflected in plasma BPN levels. Because BPN levels cannot be rapidly decreased, clients with pre-existing cirrhosis (e.g. Child Pugh class B or C) are not candidates for treatment with LAI BPN. An assessment of hepatic function (including clinical examination and liver function tests) prior to treatment initiation with LAI BPN is recommended if there are any concerns regarding pre-existing liver disease (e.g. chronic viral hepatitis and / or alcohol use disorder). Where a client 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 LAI BPN treatment.

Lower initial dose LAI BPN dosing schedule (e.g. Buvital® 8mg - 16mg weekly, 64mg monthly or Sublocade® 100mg monthly injections) should be considered for clients with significant hepatic impairment. Regular monitoring of liver function should occur for clients with persistent and severe liver disease whilst being treated with LAI BPN (e.g. clinical examination, liver function tests after 2 to 4 weeks in treatment, and at 3 - 6 month intervals once stabilised), and underlying causes (e.g. viral hepatitis, alcohol use) should be explored. Clients who develop moderate to severe hepatic impairment while being treated with LAI 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 the client should be warned accordingly.

Termination of LAI BPN treatment may be warranted if a client’s hepatic function significantly deteriorates, and specialist consultation is recommended. In one case, surgical removal of the LAI
Sublocade® was followed by improvement in liver enzymes (See 13.6 - Sublocade® product information AUS).

2.4.6 Use in clients at risk of arrhythmia

BPN has been observed to be associated with a prolonged QTc interval in some clients. Whilst in general, BPN should be avoided in clients 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 clients at risk of QT prolongation.

Key differences with LAI BPN are that average plasma levels of BPN may be consistently higher than with SL BPN (see Overview of pharmacokinetic properties). For clients at risk, more intensive workup prior to, and/or monitoring whilst on LAI BPN treatment may be required. For assessment and management see section 2.2.2 Safety and side effects - in the Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018 (1).

If there are significant concerns regarding BPN effects on QT prolongation, consider initiating and maintain treatment with SL BPN or weekly LAI 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.

2.4.7 Other medical conditions

Significant medical conditions that warrant caution with the use of LAI 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® (see 13.4 - Buvidal® Weekly product information AUS; 13.5 - Buvidal® Monthly product information AUS; and 13.6 - Sublocade® product information AUS). Assessment and management of clients with these conditions may require additional monitoring, consideration of the underlying aetiology and management plans. Where BPN treatment is required in clients with acute medical conditions such as those listed above, it may be prudent to use SL BPN treatment until the impact of BPN has been assessed, enabling easier dose titration and avoiding prolonged plasma levels from LAI’s (that cannot be reversed).

2.4.8 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®. Clients should be cautioned about driving or operating hazardous machinery until the prescriber and client are satisfied that LAI BPN does not adversely affect their ability to engage in such activities. See section 4.8 Driving
or operating machinery - in the Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018 (1).

2.4.9 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 (2).

2.4.10 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 foetal 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 they are listed as Category C medications in pregnancy (like methadone).

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

- Higher and more stable maternal blood levels of BPN than typically seen with SL 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 LAI 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 women is more likely to remain stable on LAI BPN rather than transferring to sublingual treatment (i.e. the risks of transfer to sublingual treatment may outweigh the expected benefits).

LAI BPN should be used during pregnancy only if the potential benefit justifies the potential risks to the mother and baby. See 13.3 - Pregnancy Statement – Checklist for a checklist to continue on LAI 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 in rats and other animals, including decrease in foetal weight. A dose response effect in preclinical studies is noted, with adverse effects not being reported at lower NMP levels. In animal models, the threshold for no observed adverse effect 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).

2.5 **Buvidal®**

Pregnancy and breastfeeding are listed as 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 phosphatidyl-choline 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 phosphatidyl choline has been suggested as a supplement during pregnancy (25). The maximum level of ethanol in Buvidal® (weekly product, 32mg) is less than 100mg (note: one 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 clients with liver disease, or epilepsy’ (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 LAI 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.

2.6 **Sublocade®**

Sublocade® contains BPN and N-methyl-2-pyrrolidone (NMP) and Poly DL-lactide-co-glycolide (PLGA). 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 regarding PLGA exposure during pregnancy in preclinical models (28,29). For the amounts of NMP in Sublocade® see Table 3 *List of LAI BPN excipients* below. Pregnancy and breastfeeding are not listed as contraindications in the Sublocade® Australian product information. (See 13.6 - *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).
Table 3  List of LAI BPN excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Buvidal® Weekly</th>
<th>Buvidal® Monthly</th>
<th>Sublocade®</th>
</tr>
</thead>
<tbody>
<tr>
<td>soy phosphatidyl choline [soybean]</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>glycercyldioleate</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>anhydrous alcohol</td>
<td>&lt;100mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Methylpyrrolidone</td>
<td>57-114mg</td>
<td>278-833mg</td>
<td></td>
</tr>
<tr>
<td>Poly (DL-lactide-co-glycolide)</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

2.7 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 LAI 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).

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

2.8 Breastfeeding

Pregnancy and breastfeeding are listed as contraindications to Buvidal® Weekly and Buvidal® Monthly in the Australian Product Information (3,4). Average plasma levels of BPN seen with LAI treatment may be higher than seen with SL BPN treatment (refer section 2b Overview of pharmacokinetic properties). However, it is not anticipated that this will result in significantly higher BPN levels in breastmilk. While there is no substantial literature regarding BPN exposure to infants due to breastfeeding (30) the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for LAI 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 LAI BPN rather than transferring to sublingual treatment (i.e. the risks of transfer to sublingual treatment may outweigh the expected benefits). LAI 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 contraindications in the Buvidal® European product information. Breastfeeding is not listed as a contraindication in the Sublocade® US product information.
2.9 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, gabapentinoids, 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 LAI 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 section 13.1 – Drug-Drug Interactions (DDIs).
3. Providing treatment with LAI BPN

3.1 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.

MATOD (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 clients with other health and psychosocial interventions. The key elements of MATOD are:

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

Treatment with LAI BPN formulations potentially challenges the way in which the components of MATOD services are co-ordinated and structured. Conventional MATOD 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 LAI 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 LAI BPN formulation (Buvidal® Weekly) when commencing treatment (e.g. for the first two to four weeks) until clinicians and clients become more familiar with LAI BPN treatment and individual client’s treatment needs are clarified. It is also possible, however, to commence MATOD 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 clients initiating MATOD 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 LAI versus SL BPN or methadone treatment, and when developing treatment plans with clients. It should be emphasised that safe and effective MATOD is more than the provision of medication, and that regular reviews, treatment planning, and psychosocial interventions are important elements of MATOD.

LAI 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 treatment may be provided by an approved medical specialist (addiction medicine specialist or addiction psychiatrist), doctor or nurse practitioner working in a Queensland Health Alcohol and Other Drug Service or general practice. Education is provided by insight and approvals are obtained through the Monitored Medicines Unit. Treatment support, including social and psychological support, may be provided by medical, nursing, allied health (e.g. pharmacists, psychologists and social workers), and other supporting staff including drug and alcohol workers depending on client needs and resources available.
If you’d like to know more about all treatment options including LAI BPN you can call Adis 24/7 Alcohol and Drug Support on 1800 177 833 or via http://www.adis.health.qld.gov.au/

3.2 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 client treatment goals and preferences. The assessment may take several appointments to complete. Details regarding assessing clients for MATOD are described in National and local guidelines (1,2).

Treatment planning needs to involve the client, 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 client’s substance use, physical and mental health and social issues should be developed and documented for clients.

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

3.3 Client and clinician factors in choosing LAI BPN compared with other MATOD 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 and local guidelines (1,2), and include client 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 clients. 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 no research evidence to guide the choice between the LAI BPN formulations (Buvidal® Weekly, Buvidal® Monthly and Sublocade®) and SL BPN treatment, and individual client and clinician factors need to be considered (see Table 4 Differences between SL and LAI BPN (Buvidal® and Sublocade®)).
Table 4 Differences between SL and LAI buprenorphine (Buvidal® and Sublocade®)

<table>
<thead>
<tr>
<th>Convenience of dosing</th>
<th>Sublingual formulations</th>
<th>Buvidal (weekly and monthly LAI BPN)</th>
<th>Sublocade (monthly LAI BPN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MATOD dosing requirements are determined at local jurisdictional level. In principle, treatment with SL BPN formulations require supervised dosing at the onset of treatment, with increasing access to take-away doses and unsupervised dosing according to a risk–benefit assessment. Alternate-day and three-day dosing are options for some clients – however often ineffective in clients on low daily doses (less than 8mg) or unavailable on high daily doses (24mg or more).</td>
<td>LAI BPN dosing will greatly reduce the inconvenience of regular attendance at a pharmacy / clinic for doses. This may be a particularly relevant for those who are unable to attend regularly for dosing (e.g. travel, work, childcare, mental health and homelessness).</td>
<td></td>
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<tr>
<td>Current BPN dose</td>
<td>Clients effectively treated with low daily SL BPN doses (&lt;4mg) may be unwilling to increase their ‘BPN levels’ by transitioning to LAI BPN – particularly monthly products.</td>
<td>The lowest Buvidal Weekly dose (8mg) is broadly equivalent to 4-8mg SL BPN daily; whilst the lowest Buvidal Monthly dose (64mg) is broadly equivalent to 8-12 mg BPN SL daily. Clients effectively treated with low daily SL BPN doses (&lt;4mg) may be unwilling to increase their BPN levels by transitioning to LAI doses.</td>
<td>Sublocade 100mg doses are equivalent to moderate (&gt;8mg) SL BPN doses, with the 300mg dose equivalent to doses &gt;16mg. Clients effectively treated with low daily SL BPN doses (&lt;8mg) may not be keen to increase their BPN levels by transitioning to Sublocade.</td>
</tr>
<tr>
<td>Previous exposure and experience with BPN</td>
<td>Clients 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, drug-drug interactions) warranting its discontinuation. This can generally be established rapidly with SL BPN (e.g. within seven days).</td>
<td>Clients with prior BPN treatment should have a good understanding of any likely adverse events or drug-drug interactions that will be relevant to them, and transition to LAI BPN can be confidently made after the initial 7-days of SL treatment.</td>
<td></td>
</tr>
</tbody>
</table>

Long-Acting Injection Buprenorphine in the Treatment of Opioid Dependence – Queensland Clinical Guidelines 2019 - 31 -
<table>
<thead>
<tr>
<th>Duration between doses</th>
<th>‘Single dose’ SL BPN lasts 24 hrs, with second and third daily dosing available.</th>
<th>Buvidal Weekly enables dosing every 7-10 days (and possibly up to 14 days for some clients). Buvidal Monthly enables dosing every 3-5 weeks (and possibly up to 8 weeks for some clients). Individual variation will occur.</th>
<th>Sublocade enables dosing every 26 to 42 days (and possibly up to 8 weeks for some clients). Individual variation will occur.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side effects</td>
<td>In general, adverse events to BPN are similar for both SL and LAI BPN, with the exception of injection related adverse events – which tend to be transient and mild in most cases.</td>
<td>If there are concerns regarding BPN related adverse events, particularly dose related adverse events (e.g. severe hepatic disease), clients should be initially treated and stabilised on SL BPN, allowing for assessment and management of adverse events before transitioning to LAI BPN. Moderate or severe injection related adverse events that do not spontaneously resolve are a reason to discontinue LAI BPN and transition to SL BPN treatment.</td>
<td>In general, adverse events to BPN are similar for both SL and LAI BPN, with the exception of injection related adverse events – which tend to be transient and mild in most cases.</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>In general, BPN DDIs are similar for both SL and LAI BPN formulations.</td>
<td>The ease of dose adjustment with SL BPN treatment suggests it should be preferred if there are concerns regarding potential clinically significant DDIs.</td>
<td>If concerns regarding significant DDI – consider a period of treatment with SL BPN enabling easier dose titration (and discontinuation if required).</td>
</tr>
<tr>
<td>Pregnancy and breastfeeding</td>
<td>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.</td>
<td>Due to the lack of research data on the outcomes of pregnant women and their offspring during LAI 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 LAI BPN treatment.</td>
<td></td>
</tr>
<tr>
<td>Unstable medical, psychiatric and social conditions</td>
<td>Clients with unstable clinical presentations often require frequent clinical reviews and interventions.</td>
<td>Consider Buvidal Weekly for clients that require more frequent monitoring than can be achieved with monthly doses.</td>
<td>Frequent attendance for SL BPN dosing can provide an opportunity to better engage some clients.</td>
</tr>
<tr>
<td>Concomitant medication supply</td>
<td>Adherence with concomitant medications can be enhanced through daily dosing or interval dispensing. This may be particularly relevant for clients taking medications that require high levels of adherence for effectiveness (e.g. antibiotics), or due to safety (e.g. other psychoactive medications)</td>
<td>Instalment dispensing of other medications (e.g. benzodiazepines) can be continued concurrently with LAI BPN, but this will reduce some of the benefits of LAI. However, the dispensing frequency can be adjusted to the other medication instead of being tailored to the requirement of MATOD.</td>
<td>Adherence may be linked to weekly attendance for clients on Buvidal weekly.</td>
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<tr>
<td>Cost of treatment</td>
<td>Frequent dosing increases costs for client travel. Public treatment – costs are borne by the Department of Health. Dosing at community pharmacy incurs dispensing fees and these costs are borne by the client – and usually $35-45/week.</td>
<td>Fewer transport costs for clients with less frequent attendance for dosing. Associated costs incurred by the client when they are on LAI BPN are yet to be determined.</td>
<td></td>
</tr>
<tr>
<td>Risks of non-medical medication use, for example diversion or injection</td>
<td>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).</td>
<td>Consider using LAI BPN where there are concerns regarding non-medical use (e.g. injecting, hoarding) or diversion of SL BPN (including custodial settings).</td>
<td></td>
</tr>
<tr>
<td>Takeaway / unsupervised dosing</td>
<td>‘Take-aways’ and/or unsupervised dosing regimens are appropriate for clients assessed as low risk of poor medication adherence, and to enhance client autonomy. Some clients do not meet eligibility for frequent take-away or unsupervised dosing.</td>
<td>LAI BPN may be preferred where a client 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. LAI BPN may enhance client autonomy in treatment.</td>
<td></td>
</tr>
<tr>
<td>Goal of withdrawal from MATOD</td>
<td>Withdrawal is associated with relapse to opioid use, increase in risk of opioid overdose immediately after ceasing MATOD, overdose prevention strategies (e.g. take-home naloxone), after care advised.</td>
<td>Unclear regarding whether withdrawal from LAI BPN results in better outcomes (severity and duration of withdrawal symptoms, relapse rates, deterioration health, client experience) than withdrawal from SL formulations.</td>
<td></td>
</tr>
</tbody>
</table>
4. Guideline regarding dosing regimens with LAI BPN

4.1 Commencing LAI BPN treatment

Most clients commencing LAI BPN treatment in Australia will already be in long-term treatment with SL BPN. For others initiating BPN treatment, a short period (e.g. ≥7-days) of SL BPN (as Subutex or Suboxone) is generally recommended prior to transitioning to LAI BPN treatment. This may be for three principal reasons:

- To ensure clients 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 client is satisfied with BPN treatment choice.

Local guidelines (1) should be followed when initiating SL BPN in this situation. Longer periods of SL BPN treatment may be required prior to initiating LAI BPN treatment if the client 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.

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

4.2 Transitioning from SL BPN treatment

4.2.1 Commencing treatment with Buvidal®

Clients treated with SL BPN or SL BPN-NX may be transitioned directly to Buvidal® Weekly or Buvidal® Monthly starting on the day after the last daily SL treatment dose, see recommendations in Table 5 SL and LAI Buvidal® Weekly and Buvidal® Monthly equivalent doses. Individual clinical titration of doses may be required on subsequent doses, recognising that the dose effects of the LAI are likely to increase with BPN accumulation until steady state equilibrium is achieved (usually after 3 to 5 doses). Clients can be transferred directly onto either weekly or monthly injections from SL BPN. Factors that may lead to the clinician and client 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 SL and LAI Buvidal® Weekly and Buvidal® Monthly equivalent doses).

<table>
<thead>
<tr>
<th>Daily SL BPN dose</th>
<th>Buvidal LAI weekly dose</th>
<th>Buvidal LAI monthly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6mg</td>
<td>8 mg</td>
<td>No monthly equivalent</td>
</tr>
<tr>
<td>8-10 mg</td>
<td>16 mg</td>
<td>64 mg</td>
</tr>
<tr>
<td>12-16 mg</td>
<td>24 mg</td>
<td>96 mg</td>
</tr>
<tr>
<td>18-24 mg</td>
<td>32 mg</td>
<td>128 mg</td>
</tr>
</tbody>
</table>
4.2.2 Titrating doses of Buvidal® (CS)

After selecting the appropriate weekly or monthly dose of Buvidal® (Table 5 SL and LAI Buvidal® Weekly and Buvidal® Monthly doses), clients 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 clients 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 client’s needs and clinical judgement and at doses established after initiation or switching. In previous research (12) approximately 10-20% of clients 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 LAI BPN doses – adjusting dose and frequency of doses (CS) below.

4.2.3 Supplemental or ‘top-up’ BPN doses (CS)

‘Top-up’ or supplemental doses of Buvidal® may be given if the client experiences clinical features of opioid withdrawal, cravings or persistent unsanctioned opioid use. If clinically indicated 24 hours after a Buvidal® dose, clients 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 128mg 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 LAI can be organised.

4.2.4 Buvidal® flexible dosing schedules and missed doses

Clients may be switched from weekly to monthly dosing or from monthly to weekly dosing based on the recommendations in Table 5 SL and LAI Buvidal® Weekly and Buvidal® Monthly doses above. Clients switching from weekly to monthly dosing will generally experience trough levels in the first few months similar to clients switching from SL BPN. Monitor clients 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.
4.2.5 Commencing treatment with Sublocade®

Sublocade® treatment requires preceding treatment with SL BPN product for at least seven consecutive days, preferably achieving SL doses ≥8mg daily. Longer periods of SL BPN treatment may be required prior to initiating LAI BPN treatment if the client 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 clients upon initiation is 300mg monthly for the first two months (two 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 client (e.g. clients 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 monthly 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 client. For most clients, 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 clients 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 LAI BPN doses – adjusting dose and frequency of doses (CS).
4.2.6 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 client’s opioid tolerance (e.g. client 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 client 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®
4.3 Key principles in titrating LAI BPN doses – adjusting dose and frequency of doses (CS)

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

- In general, doses should be maintained if:
  - the client 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 client is satisfied with their current dose, and requesting the dose be maintained;
  - Note that switching from 300mg to 100mg at month 3 for Sublocade® is effectively maintaining the current dose, not reducing.

- Doses should generally be reduced under the following conditions:
  - the client reports BPN dose-related adverse events (e.g. sedation or lethargy, persistent headaches, nausea, elevated liver function tests);
  - the client is seeking to reduce their dose in an attempt to ultimately withdraw from MATOD;
  - the client 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 client is not achieving desired treatment goals (e.g. persistent unsanctioned opioid use, opioid withdrawal symptoms or cravings);
  - the client does not report dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, constipation, nausea, elevated liver function tests);
  - the client reports their dose is too low and they would like a dose increase, and there are no significant clinical safety concerns.

4.4 Supplemental BPN dosing (CS)

In general, treatment with LAI BPN should not routinely require additional or supplemental BPN dosing. Wherever possible, LAI doses should be adjusted (either the dose or frequency of administration) to ensure that clients 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’ LAI BPN dose can be administered. Examples include:

- During dose titration in the early stages of LAI treatment. For example, LAI BPN doses are adjusted according to the client’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 client to be held over until their next scheduled LAI 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 LAI dosing. Clients may miss their routine dose of LAI BPN due to unforeseen circumstances. In some cases, a dose of LAI BPN can be organised to suit the conditions – however in other cases clients may not be able to access their routine LAI 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 LAI products.

- In response to other stressors or deterioration in psychological well-being. Some clients have a history of responding to a significant stressor by using substances. Sometimes, clients 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 MATOD doses under such circumstances, in practice this can be a useful short term measure to help clients through a difficult time, while working with and supporting the client to develop alternative healthy non-medication coping skills.

It should be emphasised that clients should not be maintained for more than 14 days on SL BPN treatment in addition to LAI BPN doses – adjustment of the next LAI BPN dose is recommended. If clients persistently describe their LAI BPN dose is not sufficient despite being on the maximum possible dose (e.g. 128mg Buvidal® Monthly or 300mg Sublocade®), then consider either transferring to the Buvidal® Weekly (the delivery system may make a difference) or consider discontinuing LAI treatment and resuming SL BPN or methadone treatment.

Note: If supplemental SL BPN is required, this is to be recorded on a written instruction and submitted to the Monitored Medicines Unit (MMU) following dispensing / administration.

4.4.1 Supplemental dosing for clients treated with Buvidal®

The preferred approach to supplemental dosing for clients 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 client until their next scheduled regular dose, and then to adjust the next Buvidal® dose accordingly.

However, where supplemental LAI Buvidal® cannot be used (e.g. no access to product), then additional doses of SL BPN 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 SL and LAI Buvidal® Weekly and Buvidal® Monthly doses. Consult with a medical addiction specialist or call the Alcohol and Drug Clinical Advisory Service (ADCAS) on 1800 290 928 for further advice if required. http://www.adis.health.qld.gov.au/health-professionals/adcas

4.4.2 Supplemental sublingual dosing for clients treated with Sublocade®

Whilst clients 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 client is reporting features of opioid 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).
4.5 Transfer between Buvidal® and Sublocade® (CS)

Generally, transferring clients between Buvidal® and Sublocade® should be avoided - there is no published data or clinical experience to provide recommendations on transfer between Buvidal® and Sublocade® products.

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

- Lack of availability of the formulation the client had been treated with at the new treatment site (i.e. the treatment site only has one formulation – Buvidal® or Sublocade®, and the client had been treated with the other formulation).
- Interrupted supply of one formulation (i.e. the formulation the client 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 Cmax, Cmin levels of BPN following LAI administration at steady state.

4.5.1 Transfer from Buvidal® to Sublocade®

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

4.5.2 Transfer from Sublocade® to Buvidal®

Clients on stable Sublocade® 300mg monthly doses for more than two months should transfer to Buvidal® Weekly 32mg or Buvidal® Monthly 128mg. Clients may experience a decrease in plasma BPN levels and develop opioid withdrawal and / or cravings following transfer to Buvidal®, although this is unlikely to occur given the long half-life of Sublocade®.

Clients on steady Sublocade® 100mg monthly doses, or who have only received one or two Sublocade® 300mg injections for initiation, should not experience a significant decrease in plasma 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.

4.6 Induction from other opioids: prescription opioids and methadone

Clients should be initiated onto at least 7 days of SL BPN treatment prior to initiating LAI BPN treatment. Longer periods of SL BPN treatment may be required if the client 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 the Queensland Medication-
4.7 Administering LAI 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 administered by an Australian Health Practitioner Regulation Agency (AHPRA) registered healthcare professional who has injection of schedule 8 medications within their scope of practice.

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

4.7.1 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 section 13.4 and 13.5 Buvidal® Weekly product information AUS / Buvidal® Monthly product information AUS

4.7.2 Administering Sublocade® injections

Sublocade® should be injected subcutaneously in the abdominal region between the transpyloric (Addison’s) and transtubercular planes. Injections should be given with the client 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 section 13.6 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).

4.8 Specific issues of delivering MATOD with LAI BPN

4.8.1 Intoxicated presentations

Clients 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 LAI, 6-10 hours after Buvidal® Monthly and 24 hours after a Sublocade® injection, and hence there is usually little clinical indication to withhold a LAI due to a client presenting intoxicated, in contrast to intoxicated presentations for SL BPN or methadone dosing, where peak medication effects are likely to occur whilst the client is still intoxicated. Clients 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 client is very intoxicated and unable to understand or follow instructions, the administration of the dose may be deferred and rescheduled.

### 4.8.2 Transfer of care

Particular attention is required when communicating with other health care providers regarding transfer of care for clients treated with LAI BPN. Many health care providers will initially be unfamiliar with the new LAI 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 LAI BPN injections and previous injection sites (in order to avoid injecting into same site)
- Dose and date of recent LAI BPNs ensuring details of last dose administered are included
- The formulation of LAI BPN that was administered: Buvidal® Weekly, Buvidal® Monthly or Sublocade® and the dose (in mg)
- Scheduled next dose of LAI BPN (formulation, date, dose strength and route of administration),
- Any adverse events, risks or concerns regarding LAI BPN treatment that is relevant to other health care providers

As LAI 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 LAI BPN medication may not be commonly 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.

### 4.8.3 Prescription charting

Prescribers must ensure that all prescriptions for LAI BPN are legally written, and compliant in accordance with the Queensland legislation relating to scheduled medicines.

In order for a prescription of LAI BPN to be valid it must include the prescriber’s details (name, prescriber number, place of usual practice, phone number, specialist qualifications), date of the prescription, date for supplying the medication (if applicable), client’s details (name, address, date of birth), name of buprenorphine product including the name and strength of the product (e.g. Buvidal® Weekly 16mg; Sublocade® 100mg); the dose (in numbers and words), route of administration and instructions about using the medicine.

The prescriber must document that the dose is to be dispensed to the client, however the medication is never supplied directly to the client or their carer. The medication is delivered and supplied directly to the health care provider for administration.
5. Discontinuing LAI BPN treatment

Various scenarios for discontinuing LAI BPN treatment are possible:
   a. Withdrawing off LAI BPN (with goal of opioid abstinence)
   b. Transfers to SL BPN
   c. Transfer to methadone / other opioid analgesics
   d. Transfer to oral naltrexone

5.1 Withdrawing off LAI BPN (with goal of abstinence)

Many clients in MATOD are keen to achieve abstinence, discontinue opioid treatment and withdraw from opioids. Unfortunately, most clients attempting withdrawal from MATOD relapse to unsanctioned opioid use and are at increased risk of opioid overdose with as few as 10-20% of clients successfully achieving opioid abstinence in the short to medium term. Whilst some clients 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. Successful withdrawal from MATOD is more likely in clients who: have stopped 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), and who undertake planned gradual rather than precipitous reduction regimens on methadone or BPN. These conditions are most likely relevant for clients attempting withdrawal from LAI BPN treatment also.

There is very little experience, and no studies examining withdrawal from LAI buprenorphine treatment. The onset, peak and duration of withdrawal symptoms is likely to be variable between clients, and according to the duration of prior LAI BPN dosing. In general, withdrawal syndrome from LAI 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 LAI BPN products. Table 6 Timeframe plasma BPN undetectable following discontinuation of long-term LAI BPN treatment highlights the time frame for plasma BPN levels to drop to sufficiently low levels for the emergence of significant withdrawal features following long-term (steady state) LAI BPN doses, although considerable individual variability may be expected.

<table>
<thead>
<tr>
<th>LAI BPN</th>
<th>Half-life (at repeated doses)</th>
<th>Likely timeframe for onset of withdrawal symptoms after last maintenance LAI dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublocade® 100mg doses</td>
<td>43-60 days</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Sublocade® 300mg doses</td>
<td>3-9 months</td>
<td></td>
</tr>
<tr>
<td>Buvidal® Weekly</td>
<td>3-5 days</td>
<td>Up to 2-3 weeks after last dose</td>
</tr>
<tr>
<td>Buvidal® Monthly</td>
<td>19-25 days</td>
<td>Up to 2-3 months after last dose</td>
</tr>
</tbody>
</table>
Clients who have been on treatment for long enough to achieve steady state plasma levels of LAI 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 LAI BPN treatment for shorter periods.

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

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

As in attempts to withdraw from other forms of MATOD, 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 (1,2), however caution should be used with extended use (beyond a few days) of sedatives or hypnotic medications.

Clients who have withdrawn from LAI BPN should be strongly encouraged to access supplies of take-home naloxone.

### 5.2 Transfers to SL BPN (CS)

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

#### 5.2.1 For Sublocade® to SL BPN

Recommended practice is to initiate SL BPN with low doses at approximately the time of the next scheduled LAI 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 LAI BPN concentrations gradually subside, aiming to achieve the expected SL dose based on dose conversion tables. Frequent clinical reviews are recommended.

#### 5.2.2 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>
<thead>
<tr>
<th>Table 7 SL and LAI Buvidal® Weekly and Buvidal® Monthly doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buvidal® Weekly LAI dose</strong></td>
</tr>
<tr>
<td>8mg</td>
</tr>
<tr>
<td>16mg</td>
</tr>
<tr>
<td>24mg</td>
</tr>
<tr>
<td>32mg</td>
</tr>
</tbody>
</table>
5.3 Transfer to methadone or other opioid analgesics (CS)

There is little clinical experience and no published studies regarding transfer from LAI BPN to methadone. Given this lack of evidence, clients seeking to transfer from LAI 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 Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines (1) initiating at low doses 20-30mg daily, reviewing regularly and titrating accordingly).

If a client has to discontinue all BPN treatment abruptly (e.g. due to a severe adverse event, or client unwillingness to continue any BPN treatment), transition to methadone may be considered after consultation with a medical addiction specialist or call ADCAS on 1800 290 928 for further advice. The general principle is to recommence low dose methadone (e.g. 20mg oral daily doses) at the time of the next proposed LAI dose, regularly monitor the client (at least weekly), and carefully increase the dose (by no more than 5mg intervals) after clinical reviews until the methadone dose and client have stabilised, recognising that residual BPN from LAI 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.

5.4 Transfer to oral naltrexone (CS)

Transfer to oral naltrexone should be possible after BPN effects have subsided – generally 2-4 weeks after weekly LAI BPN and 4 to 12 weeks after the last dose of monthly LAI BPN (but possibly up to 6 months for clients 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. Low naltrexone 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 medical addiction specialist or ADCAS on 1800 290 928 if any concerns.
6. Clinical conditions

6.1 Overdose

Whilst BPN alone 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, benzodiazepines and gabapentinoids. 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 LAI 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 LAI BPN formulations, however the prolonged duration of BPN effects with LAI formulations requires clients to be clinically monitored for extended periods of time, until the client has clinically recovered, and may require prolonged monitoring and a naloxone infusion in a hospital setting.

6.2 Polydrug use and regular intoxication

The issue of administering LAI BPN doses to an intoxicated client is addressed in section Specific issues of delivering MATOD with LAI BPN. Specific interventions may be required for clients with harmful patterns of other substance use – such as alcohol, benzodiazepines, gabapentinoids, stimulants, cannabis and/or injecting drug use. These are described in National Guidelines for Medication-Assisted Treatment of Opioid Dependence (2). Clients with patterns of regular and harmful substance use often benefit from regular clinical monitoring and review, which may be more difficult to schedule in clients attending for dosing only once a month. If more frequent clinical reviews are required and the client has a history of non-attendance for scheduled appointments, then a medication option with a more frequent dosing interval may be considered. Clients with heavy and regular/dependent patterns of use of alcohol, benzodiazepines, gabapentinoids 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.

6.3 Acute pain management for clients in LAI BPN treatment

Clients on MATOD 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 clients 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 clients’ 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 similar or higher mu intrinsic activity than BPN;
c) use of parenteral BPN (e.g. Temgesic®) for breakthrough pain; and/or
d) non-opioid analgesic approaches such as ketamine infusions or regional analgesia;

Similar approaches can be used for clients with LAI BPN treatment to achieve analgesia in acute/emergency situations. It is not possible to cease BPN in clients treated with LAI BPN formulations without surgical removal of the LAI BPN. If a client with LAI BPN presents to a general practitioner with severe acute pain, they may need to be referred to an emergency department due to complexity or the GP may need to consult with a medical addiction specialist or ADCAS on 1800 290 928.

Persistent pain should be managed with an emphasis on psychosocial and non-opioid pharmacological approaches. Non-pharmacological strategies can include client education about healthy lifestyle modifications including a daily routine of structured activities incorporating sleep, nutrition, adequate exercise, social interaction and rest. Client education regarding the links between tobacco and pain may be indicated with discussion about quitting. Non-opioid pharmacological options might include simple analgesia like paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and/or adjuvant medications, such as anticonvulsants and antidepressants. Benzodiazepines can exacerbate pain in the longer term and should only be considered for extremely short episodic use (1).

A common issue experienced by opioid dependent clients is dental pain. It is recommended that dental pain is managed in line with recommendations for persistent pain, with preference towards non-pharmacological treatments and simple analgesia rather than additional pharmaceutical opioids (1).

6.4 Chronic pain management for client in LAI BPN treatment

Chronic pain is common amongst clients in MATOD (estimated at between 30 to 60% of clients) 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 clients in methadone or BPN treatment, general principles of chronic pain management should be followed (33), and include client education and engagement in the treatment process, appropriate use of opioid and non-opioid medications (e.g. antidepressants, NSAIDs, paracetamol, gabapentinoids), 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 clients with concurrent chronic pain, and it is expected that LAI BPN formulations will also be effective as part of treatment plans in managing comorbid chronic pain in dependent opioid users. LAI BPN should not be used in conjunction with other opioid analgesics (e.g. morphine, fentanyl, codeine) in chronic pain management, given its ‘blockade’ effect.

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

6.5 Surgical removal of LAI BPN

Data on surgical removal of Buvidal® is not available.

In the event the LAI Sublocade® dose must be removed, it can be surgically excised under local
anaesthesia within 14 days of injection. Only the most recently-injected LAI BPN can be removed. The surgical procedure requires a small incision in the abdomen where the LAI was placed, removal of the LAI with forceps, and suturing to close the incision. The removed LAI should be handled with adequate security, accountability, and proper disposal, according to Queensland legislation relating to scheduled medicines. The residual plasma concentrations from previous injections will decrease gradually over subsequent months. Clients who have the LAI removed should be monitored for signs and symptoms of withdrawal and treated appropriately (30).
7. **Use of LAI BPN for withdrawal treatment**

There is considerable interest among clients and clinicians in the use of LAI 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 clients in their attempts at opioid withdrawal. However, at this time there is little clinical experience or research evidence to inform the use of LAI BPN for managing opioid withdrawal, and further research is required. Consultation with a medical addiction specialist or ADCAS on 1800 290 928 is recommended.
8. Special populations and settings

8.1 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, geographical remoteness) and demographic backgrounds (Aboriginal and Torres Strait Islander people, culturally diverse backgrounds, women, LGBTI people, prisoners, older people) that can greatly impact upon the experience of engagement of clients with opioid treatment (and other service) providers. The introduction of LAI BPN treatment that allows for dosing on a monthly basis may enhance client autonomy but may detract from the ability to engage the client with treatment and other services. Particular attention to informed consent to treatment with LAI 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.

8.2 Hospital and correctional problems

Many clients in MATOD 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 LAI BPN treatment. Nevertheless, careful co-ordination between hospital and correctional staff with LAI BPN treatment providers will be required.

8.2.1 Correctional settings

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

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

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

Clients on MATOD in Queensland correctional centres are commonly released into the community unexpectedly via courts (outside control of health). LAI BPN having longer dosing windows may allow greater flexibility to arrange community dosing and provide transfer of care documentation. Clients on LAI BPN leaving custody should be provided education re the persistent clinical effects LAI BPN.

As LAI 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 of several months.
8.3 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 clients in MATOD due to concerns regarding methadone or BPN dispensing or storage of take-away doses. Treatment with LAI BPN provides an opportunity for MATOD to be better integrated into these settings, with either the client attending the dosing site or, if possible, the LAI BPN service providers attending the rehab/housing service.
9. **Managing travel**

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

9.1 **Local travel**

The duration of action of LAI BPN should make local travel less problematic for clients. 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.*

9.2 **Interstate travel**

See section 6.9.2 of the Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines (1) re interstate transfers. Beyond interstate sites having access to Buvidal® and/or Sublocade®, there are no additional requirements.

9.3 **Overseas travel**

As Buvidal® and Sublocade® cannot be given to clients, overseas travel will require transferring clients 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 clients can be observed during transfer from LAI 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. **Client information and perspective**

LAI BPN should always be presented as one choice in the range of currently available MATOD – clients may need lots of information and reassurance from their clinicians as they consider whether LAI BPN will be compatible with their lifestyle.

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 client’s treatment goals as the expert in their own life.

Clients need to be armed with a wide range of information about LAI BPN, which 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 process involved in transferring from other MATOD and whether 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 by:

- recognising that this new product will not suit everyone and that a choice of MATOD is ideal;
- listening to, taking seriously and acting promptly when your clients 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 ADCAS on 1800 290 928 for support;
- listening to people’s stories, goals, challenges and expectations;
- advising and guiding your client to assist them get the best fit;
- encouraging them to compile a list of advantages and disadvantages to help them with their decision-making;
- offering a move to LAI BPN as a trial, reassuring your client that they will be able to return to SL BPN or methadone liquid if LAI BPN does not suit them;
- respecting your client’s decision to not try LAI BPN;
- making sure the client 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.

Many clients will find LAI BPN 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. You can set your client up for success by:

- discussing expectations about the therapeutic relationship to maximise the usefulness of LAI BPN;
- encouraging frank communication with your client;
- 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 client 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, especially if the client is moving from regular contact with a
explaining that they should not drive or operate heavy machinery while they are getting used to the new formulation;

- encouraging clients 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 clients have access to the consumer guidelines and special interest guides, including the guide to LAI BPN.

Some clients have particular needs. Being sensitive to the diversity of clients in treatment 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;
- Recognising that some consumers transferring from correctional facilities may need different responses in the community than they did when incarcerated.

The best therapeutic relationships are built on co-operation, unbiased information sharing and honest and open communication that balances your clinical responsibilities with your client’s treatment goals.
11. Governance

11.1 Acquisition
An approved QOTP prescriber can obtain LAI BPN from a licensed wholesaler on a compliant purchase order from the prescriber, in accordance with the Queensland legislation relating to scheduled medicines.

11.2 Storage

11.2.1 Buvidal®
Buvidal® injections are required to be stored below 25°C. Do not refrigerate or freeze. To comply with storage requirements for Schedule 8 medicines, Buvidal® injections must be kept securely, in accordance with the Queensland legislation relating to scheduled medicines.

11.2.2 Sublocade®
Sublocade® injections are required to be stored refrigerated at 2-8°C. Once outside the refrigerator this product may be stored in its original packaging at room temperature, less than 25°C, for up to seven days prior to administration. To comply with storage requirements for Schedule 8 medicines, both in and out of refrigeration, Sublocade® injections must be kept securely, in accordance with the Queensland legislation relating to scheduled medicines.

11.3 Authority to prescribe and administer LAI BPN
Approval to prescribe LAI BPN must be granted by the Monitored Medicines Unit (MMU) under the provisions of the state legislation before commencing treatment.

All clientscommencing treatment with LAI BPN must be registered on the Queensland Opioid Treatment Program. When transferring from SL BPN to LAI BPN, a new admission form noting change of drug type to LAI BPN is required to be submitted to the MMU.

Records of all incoming and outgoing stock of Schedule 8 medicines must be kept in accordance with the Queensland legislation relating to scheduled medicines.

The prescriber must document in the client’s clinical record each time they prescribe and administer the LAI BPN. The documentation should include the following particulars:

- prescribers name, prescriber number, phone number, specialist qualifications;
- client’s name and date of birth;
- date of prescribing and date of administration;
- drug name (including the brand name), dose, route of administration;
- site of administration;
- instructions about using the medicine.
11.4 Disposal of Schedule 8 medicines

Any unused Schedule 8 medicines must be disposed of in accordance with the Queensland legislation relating to scheduled medicines.

For further information on Queensland legislation requirement relating to Schedule 8 medicines, please contact your local Public Health Unit.

12. References


31. Treatment Improvement Protocol 63, Medications for Opioid Use Disorder - For Healthcare Addiction Professionals, Policymakers, patients and Families: Substance Abuse and Mental Health Services


## 13. Appendices

### 13.1 Drug-Drug Interactions (DDIs)

*Drug-drug interactions of potential clinical relevance with LAI BPN*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug(s) within Class</th>
<th>Clinical effect and suggested management</th>
</tr>
</thead>
</table>
| Benzodiazepines and Other Central Nervous System (CNS) Depressants | Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, and other opioids | - Increases the risk of respiratory depression, profound sedation, coma, and death  
- Use of these substances should be avoided or minimised during treatment with buprenorphine formulations. Clients should be advised of the extreme danger of concomitant use of sedatives while receiving LAI BPN treatment. |
| CYP3A4 inhibitors:                                   | Macrolide antibiotics  
protease inhibitors (e.g. erythromycin, ketoconazole, ritonavir, nelfinavir, indinavir, itraconazole) | - An interaction study of buprenorphine with ketoconazole resulted in increased Cmax (approximately 50%) and AUC (approximately 70%) of buprenorphine and, to a lesser extent, of the metabolite, norbuprenorphine  
- Clients 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.  
- Monitor for buprenorphine withdrawal if the concomitant medication is discontinued after the client is stable on LAI BPN. |
| CYP3A4 Inducers                                      | Rifampcin  
Carbamazepine  
Phenytin  
Phenobarbital                                               | - 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 clients 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.  
- Monitor for signs and symptoms of buprenorphine toxicity or overdose, if the CYP3A4 inducers is discontinued after the client is stable on LAI BPN. |
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<tr>
<th>Drug Class</th>
<th>Drug(s) within Class</th>
<th>Clinical effect and suggested management</th>
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| **Antiretrovirals:** Non-nucleoside reverse transcriptase inhibitors (NNRTIs) | Efavirenz, Nevirapine | - Significant pharmacokinetic interactions between NNRTIs and sublingual buprenorphine have been shown, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.  
- Monitor for increase or decrease in therapeutic effects of NNRTIs. |
| **Antiretrovirals:** Protease inhibitors (PIs) | Atazanavir, Ritonavir | - Treatment with atazanavir or atazanavir/ritonavir may result in elevated levels of buprenorphine  
- If atazanavir +/- ritonavir is initiated once the client is stable on LAI BPN, monitor for signs and symptoms of over-medication with buprenorphine. If necessary, reduce LAI BPN dose from 300 to 100mg, or discontinue LAI BPN and treat with sublingual buprenorphine to enable rapid dose adjustments. |
| **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) | - May result in serotonin toxicity in high doses (e.g. overdose) or when multiple serotonergic drugs are combined. Monitor for signs and symptoms of serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug. |
| **Monoamine Oxidase Inhibitors (MAOIs)** | e.g. Phenelzine, tranylcypromine | - MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).  
- It is recommended that clients receiving buprenorphine and MAOI should be closely monitored.  
- Exacerbation of the opioid effects based on experience with morphine |
| **Diuretics** | | - May reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.  
- Intervention: Monitor clients for signs of diminished diuresis and/or effects on blood pressure, oedema or cardiac failure and increase the dosage of the diuretic as needed. |
| **Anticholinergic Drugs** | | - May increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.  
- Monitor for signs of urinary retention or reduced gastric motility. |
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<th>Drug Class</th>
<th>Drug(s) within Class</th>
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| Opioid antagonists | Naltrexone, Naloxone     | - Opioid antagonists should generally not be used outside of emergency situations in clients in opioid agonist treatment, including LAI BPN.  
- Naloxone may be administered in response to an opioid overdose, multiple injections or an infusion of naloxone may be required.  
- For opioid-dependent clients currently receiving buprenorphine treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For clients currently receiving naltrexone treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone. |
| Opioid analgesics | Opioids                   | - Buprenorphine may reduce the effects of opioid analgesics through receptor blockade. Clients 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  
- Adequate analgesia may be difficult to achieve when administering a full opioid agonist in clients 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.  
- Titrate opioid analgesics according to clinical response.  
- Call ADCAS on 1800 290 928 for advice on complex cases. |
| Gabapentinoids  | Gabapentin, pregabalin, baclofen | - 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. Clients should be cautioned to use gabapentinoids concurrently with this product only as directed by their physician. |
| Alcohol        | Alcoholic drinks or medications containing alcohol | - Alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of buprenorphine |
13.2 LAI BPN Studies

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<tr>
<th>Study Reference</th>
<th>Product</th>
<th>Setting</th>
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<tr>
<td>NCT02672111</td>
<td>Buvidal®</td>
<td>Community AUS</td>
<td>Frost et al 2019</td>
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<tr>
<td>HS-14-499 (Braeburn)</td>
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**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 adverse events 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.
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 in-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)
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 nornbuprenorphine, 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 (Cmax and AUC0–7d), with time to Cmax ~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)

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.

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.

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)
**Background:** RBP-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.

**Methods:** 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.

**Findings:** 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 (p<0·0001 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.

**Interpretation:** 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).
**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 μ-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.
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 (7)
**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 tmax 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.

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<th>Study Reference</th>
<th>Product</th>
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<td>ISRCTN24987553</td>
<td>Buvidal®</td>
<td>Community</td>
<td>Albayaty et al 2017</td>
</tr>
</tbody>
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13.3 Pregnancy statement – checklist

Pregnancy Statement – Checklist of issues to be discussed with pregnant clients

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

- clients should be involved in decision making regarding their treatment;
- opioid agonist treatment is first line treatment for opioid dependence during pregnancy;
- optimal ante-natal care for pregnant women who are on opioid agonist treatment includes regular liaison between their opioid 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, the following points should be adequately documented in the clients’ clinical file:

- 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, and Sublocade® in Australia by the Therapeutic Goods Administration;
- the client has been involved in a discussion regarding their treatment decision including risks and benefits and has agreed to continue depot buprenorphine treatment.

13.4 Buvidal® Weekly product information AUS

13.5 Buvidal® Monthly product information AUS

13.6 Sublocade® product information AUS

13.7 Sublocade® prescribing information US