Brief clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence

VICTORIA State Government | Health and Human Services

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Introduction

This brief guideline is to be used in conjunction with the full version of the *Policy for maintenance pharmacotherapy for opioid dependence* (Victorian Government Department of Health and Human Services) and with the *National guidelines for medication-assisted treatment of opioid dependence* 2014.

Abbreviations

AE	Adverse event
BPN	Buprenorphine
DDI	Drug–drug interaction
SC	Subcutaneous
SL	Sublingual

About depot buprenorphine products: Buvidal® and Sublocade®

This brief clinical guideline will help clinicians and clients make decisions about using the following long-acting injected depot buprenorphine (depot BPN) preparations.

Buvidal is a modified release formulation of BPN, registered in Australia for 'maintenance treatment of opioid dependence within a framework of medical, social and psychological support'. Buvidal is designed to be administered by subcutaneous 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 – 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL or 32 mg/0.64 mL BPN as the active ingredient.
- Buvidal Monthly is available in three dose strengths in prefilled syringes with a 23-gauge needle: 64 mg/0.18 mL, 96 mg/0.27 mL or 128 mg/0.36 mL BPN as the active ingredient.

Sublocade is an extended-release formulation of BPN, administered monthly by subcutaneous (SC) injection and provides sustained plasma levels of BPN over the monthly dosing interval.

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

Framework for treatment with depot BPN products

The key elements of safe and effective BPN treatment for opioid dependence are:

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

Patients need accurate information and options regarding their medication and treatment, as part of informed decision making and consent. Once-a-week and once-a-month depot injections reduce the need for daily supervised and/or take-away doses of sublingual (SL) BPN formulations.

Potential benefits of depot BPN treatment include:

- greater convenience for patients in that they will not have to attend dosing sites (pharmacies, clinics) on a frequent basis for supervised dosing
- reduced treatment costs
- greater medication adherence and enhanced treatment outcomes for some patients who struggle to attend regularly for dosing with SL BPN
- less risk of diversion and non-medical use of the medication, enhancing community safety.

However, BPN formulations may not suit all patients, and some will prefer SL BPN or methadone treatment, and these options should be available.

Buvidal and Sublocade should be administered by registered health practitioners. Buvidal and Sublocade medications should not be handled by, or dispensed to, patients or carers.

Delivering treatment with depot BPN

Table 1 shows the key characteristics of Buvidal and Sublocade and recommended dosing regimens.

Specific recommendations regarding medication regimens for each product are described below.

See the full guidelines and product information for an overview of the clinical pharmacology, evidence of safety and efficacy of these products, and issues regarding special populations.

There is no evidence directly comparing the safety or efficacy of Buvidal and Sublocade products.

Dosing recommendations for Buvidal

Transferring from SL BPN. Patient should usually be treated with seven or more days of SL BPN prior to transferring to Buvidal, with either Buvidal Weekly or Buvidal Monthly starting on the day after the last daily SL dose. Buvidal doses are 'matched' to SL BPN doses as shown in Table .

Table 1: Dose conversions between SL BPN, depot Buvidal Weekly and Buvidal Monthly doses

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

Patients should be reviewed prior to the next scheduled dose and assessed for adverse events, withdrawal, cravings, substance use and patient's rating of dose adequacy.

Titrate doses upwards or downwards accordingly. Steady-state equilibrium is usually achieved after three to four doses.

Commencing BPN treatment with Buvidal

While not recommended as routine practice, Buvidal Weekly can be initiated directly from short-acting opioids (such as heroin) or after fewer than seven days of SL BPN treatment (for example, the patient unable to access dosing sites for daily SL dosing). For patients reporting current dependent opioid use, initiate Buvidal Weekly 24 mg doses and review for subsequent dose titration.

Flexible dosing schedule

Patients may switch between Buvidal Weekly and Buvidal Monthly (see Table). Individual dose adjustment may be required.

- Buvidal Weekly doses may be given up to two days before or after the weekly time point (days five to nine)
- Buvidal Monthly may be given up to one week before or after the monthly time point (weeks three to five).

If a dose is missed, the next dose should be administered as soon as possible. Re-induction may be required if more than 14 days have elapsed between Buvidal Weekly doses, or more than eight weeks between monthly doses.

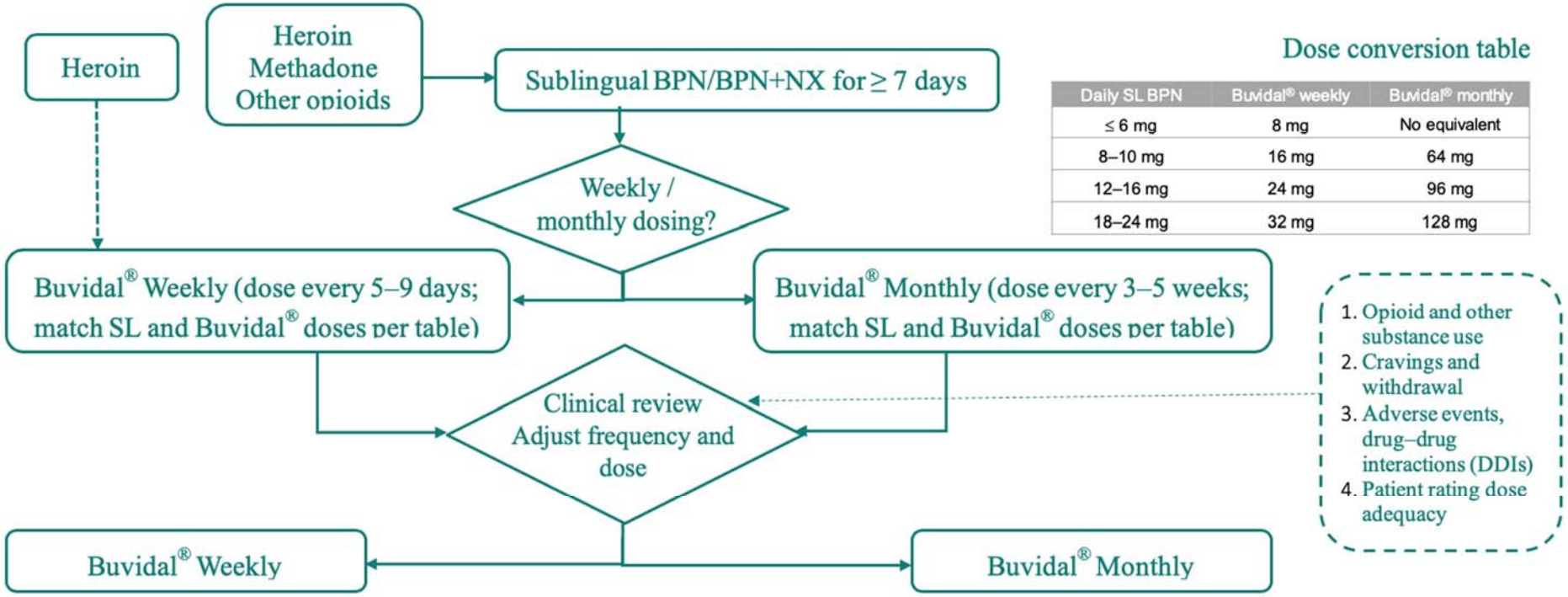
Supplemental or top-up BPN doses

Supplemental Buvidal injections may be used if clinically indicated (patient experiencing opioid withdrawal, cravings or persistent unsanctioned opioid use).

Patients may receive additional 8 mg Buvidal Weekly injections at least 24 hours apart, to a maximum total weekly dose of 32 mg, and maximum total monthly dose of 128 mg.

If supplemental Buvidal® Weekly doses cannot be administered, supplemental doses of SL BPN (≤ 8 mg daily) may be used for a limited period of time until the next depot injection can be organised.

Figure 1: Overview dosing with Buvidal



Dose conversion table

Daily SL BPN	Buvidal® weekly	Buvidal® monthly
≤ 6 mg	8 mg	No equivalent
8–10 mg	16 mg	64 mg
12–16 mg	24 mg	96 mg
18–24 mg	32 mg	128 mg

Dosing recommendations with Sublocade

Commencing Sublocade treatment

Sublocade treatment requires preceding treatment with SL BPN for at least seven days, preferably achieving SL doses ≥ 8mg daily.

Sublocade is generally not recommended for patients on daily SL BPN doses < 8mg.

The first Sublocade dose should usually be administered approximately 24 hours after the last SL BPN dose but may be administered on the same day.

For most patients, commence 300 mg doses for the first two months (two x monthly doses), reflecting 'loading' doses that elevate plasma BPN levels more rapidly than the initial treatment period.

Sublocade may be initiated with 100 mg doses where there may be safety concerns of high BPN plasma levels (e.g. severe hepatic disease, DDIs).

After the initial two monthly Sublocade doses, select between 100 mg or 300 mg four-weekly doses.

For most patients, 100 mg four-weekly Sublocade doses will be adequate, maintaining plasma levels (at steady state equilibrium) achieved with the first two 300 mg 'loading' doses.

Maintenance 300 mg doses should be considered for those patients who had previously stabilised on high-dose SL BPN (e.g. 24 to 32 mg daily), or continue to experience cravings, withdrawal or unsanctioned opioid use during the first two-month period of Sublocade dosing or with 100 mg Sublocade doses.

Sublocade flexible dosing schedules

Sublocade doses can be administered up to two days ahead of a scheduled dose (that is, 26 days since the last injection), or up to 14 days after the 28 day interval (that is, to 42 days since the last injection) without dose adjustments.

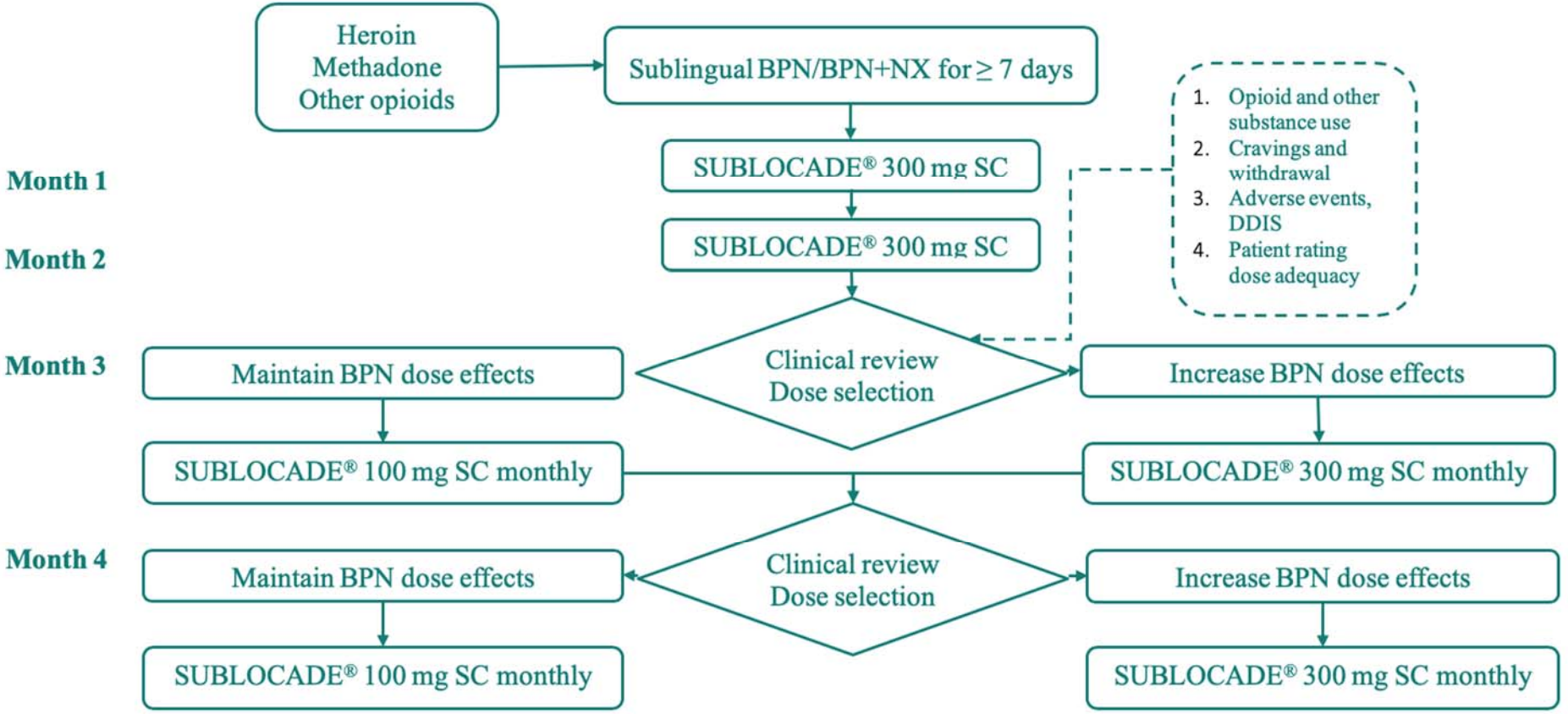
If a dose is missed, the next Sublocade dose should be administered as soon as practically possible. Re-induction may be required if more than eight weeks between Sublocade doses has elapsed.

Supplemental or 'top up' BPN doses

Supplemental SL BPN doses may be given if clinically indicated (patient experiencing opioid withdrawal, cravings or persistent unsanctioned opioid use).

Additional SL BPN (≤ 8 mg daily) may be used for a limited period of time until the next depot injection can be organised.

Figure 2 Overview dosing with Sublocade



Safety issues regarding use of depot products

Precautions and contraindications

Depot products should not be administered to anyone hypersensitive to BPN or any of the excipients of Buvidal or Sublocade (see product information for details).

Precautions regarding the use of Buvidal and Sublocade are similar to treatment with SL BPN and include patients with high-risk sedative use (for example, alcohol, benzodiazepines), severe hepatic disease, cardiac arrhythmias and respiratory depression (see product information for details).

Adverse events (AEs)

Both depot products can be associated with local injection-site AEs – redness, pain, tenderness and swelling in 5–10 per cent of patients.

These are usually mild, transient and resolve spontaneously.

Sublocade doses appear to be more commonly associated with a palpable lump at the injection site, which dissolves with time.

Systemic AEs as per SL BPN (for example, nausea, headache, constipation).

Drug–drug interactions (DDI)

DDIs are expected to be the same as for SL BPN, however the long duration of depot BPN effects may result in prolonged DDI.

If there are concerns, stabilise the person on SL BPN and monitor DDI before transferring to depot BPN products.

Pregnancy and breastfeeding

SL BPN has an acceptable safety profile and is effective in pregnancy.

There is a lack of research data on the safety and effectiveness of depot BPN formulations in pregnancy and breastfeeding.

A neonatal opioid withdrawal syndrome is likely to occur.

Pregnant women on depot BPN should be transferred to SL BPN, although may be continued on depot products if the potential benefit justifies the potential risks to the mother and baby.

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.

Patients should be cautioned about driving or operating hazardous machinery.

Withdrawal from depot BPN products

The prolonged duration of action of the depot products means that withdrawal symptoms are likely to emerge long after the last depot dose.

Withdrawal features may emerge four to 12 weeks after last Buvidal Monthly dose, or one to four weeks after the last Buvidal Weekly dose.

Peak withdrawal features may emerge four to 24 weeks after last 300 mg dose or four to 12 weeks after last 100 mg dose.

Withdrawal symptoms may persist for weeks (or months), and are expected to be less severe than withdrawal from shorter-acting opioids.

However, there is little documented experience of withdrawal from depot BPN products.

It is generally recommended to taper the depot dose to the lowest possible before discontinuing treatment, and to review the patient at regular intervals.

Administration of depot products by other routes

Both depot products are intended for subcutaneous administration and **should never be injected intramuscularly, intra-dermally, intravenously or intra-arterially**.

For this reason, depot formulations must be administered by a suitable healthcare professional, and never be dispensed or supplied directly to the patient or carer.

Transfer from methadone

There is limited experience and no documented evidence regarding transferring patients from methadone directly to depot BPN products. Transfer to SL BPN is recommended for at least seven to 14 days prior to commencing depot treatment.

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

	SL Suboxone and Subutex	Buvidal Weekly and Monthly	Sublocade
Formulations	Suboxone contains buprenorphine (BPN) and naloxone in 4:1 ratio 2/0.5 mg and 8/2 mg sublingual film Subutex contains buprenorphine in 0.4 mg, 2 mg and 8 mg sublingual tablets	Buvidal Weekly and Monthly contain BPN in FluidCrystal® injection depot technology Subcutaneous (SC) injections in prefilled syringes with 23-gauge needle. Administration via upper arm, thigh, abdomen or buttocks Buvidal Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL; 32 mg/0.64 mL Buvidal Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL; 128/0.36 mL	Sublocade contains BPN in the ATRIGEL® delivery system SC injections in prefilled syringes with 19-gauge needle administered in abdomen Monthly doses: 100 mg/0.5 mL or 300 mg/1.5 mL
Storage requirements	Store at room temperature (below 30° C)	Store at room temperature (below 25° C) Do not refrigerate or freeze.	Cold storage requirements (2–8°C). May be stored at room temperature (below 30°C) for up to 7 days before use. Remove from cold storage for at least 15 minutes prior to SC injection
Clinical pharmacology	Bioavailability 10–30% Onset effects within 1 hour, with peak effects 2-4 hours after dose Duration effects usually 24 hours but dose dependent and can vary from 8 to 72 hours	Bioavailability = 100% Time to peak plasma level (t_{max}) Buvidal Weekly = 24hrs Buvidal Monthly = 6–10 hrs Half life Buvidal Weekly = 3–5 days Buvidal Monthly = 19–25 days Steady-state equilibrium by 4th dose	Bioavailability = 100% Time to peak plasma levels ((t_{max}) = 24hrs Half-life = 43 to 60 days Steady-state equilibrium by 4th (300/100 mg) to 6th dose (300/300 mg)
Frequency of dosing	Daily, two or three day doses Take-aways and unsupervised dosing available for low risk	Buvidal Weekly dose can be administered every 7±2 days (5–9 day schedule) Buvidal Monthly dose can be administered every 4±1 weeks (3–5 week schedule)	Sublocade dosed every 4 weeks (26–42 day schedule)
Key drug–drug interactions (DDIs)	Systemic BPN DDI include: Opioids agonists: can reduce effects other opioids (blockade); BPN may precipitate withdrawal on induction Sedatives (e.g. benzodiazepines, alcohol, TCAs, antipsychotics,	As for SL Suboxone and Subutex	As for SL Suboxone and Subutex

	SL Suboxone and Subutex	Buvidal Weekly and Monthly	Sublocade
	gabapentinoids): sedation, respiratory depression, overdose A number of potential DDI can occur but are rarely of clinical significance (e.g. interactions with medications that induce or inhibit CYP450 and can lower or increase BPN plasma levels); or are rare (e.g. serotonergic syndrome in combination with medication such as SSRIs, MAOIs, tramadol; or medications that can cause QT prolongation and increase risk of cardia arrhythmias). Long duration of effects of depot BPN products precludes timely dose adjustment for DDI. If concerned re: potential DDI – initiate treatment with 'short acting' SL BPN for 1-4 weeks, monitor DDI and adjust medications accordingly, prior to transfer to depot injection.		
Recommended dosing regimen Commencing treatment	From heroin, morphine: Commence 8 mg Day 1 when patient in early / mild opioid withdrawal (usually > 8–12 hrs after last dose or use). Titrate upwards on daily basis as required. From methadone: Initiate BPN when patient in moderately severe withdrawal (e.g. COWS ≥ 12) (e.g. 1–2 days after last methadone dose) Day 1: 2 mg + 6 mg after 1–2 hrs, with additional 2–8 mg doses every 2–4 hrs as required to alleviate opioid withdrawal	Buvidal dose should be determined according to patient's SL BPN dose (see Table 1: Dose conversions between SL BPN, depot Buvidal Weekly and Buvidal Monthly doses). Titrate subsequent doses after clinical review. Note increasing effects during first few doses (accumulation to steady state after about 4 doses) Buvidal may be initiated directly (without transition via SL BPN) if required. Initiate 24 mg Buvidal Weekly dose, and titrate dose until stable.	Initiate treatment with SL BPN (at least 8 mg) for ≥ 7 days, then transfer to Sublocade. Recommended induction: 300 mg monthly injections x 2 doses (8 weeks) then 100 mg monthly doses (if patient 'stable' on initial 2 x 300 mg doses) or 300 mg monthly doses if require additional BPN effects (e.g. cravings, withdrawal, continued opioid use) Patients may be initiated with 100mg Sublocade (after at least 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 patients on low dose SL BPN

	SL Suboxone and Subutex	Buvidal Weekly and Monthly	Sublocade
	Day 2 onwards: titrate BPN dose daily as required.		(< 8mg), and Buvidal should be preferred for such patients.
Maintenance phase	Adjust dose to achieve treatment goals (reduced use of other opioids, reduced withdrawal and cravings; blockade effects). Range 2-32mg daily; most patients require 12-24mg daily	Titrate dose to achieve treatment goals. Adjust doses when transferring between weekly and monthly doses	Titrate dose to achieve treatment goals. 100mg or 300mg monthly injections.
Withdrawal phase	Gradually taper dose over several weeks-months (e.g. 2–4 mg weekly reductions)	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).	Reduce dose to 100 mg monthly injections prior to stopping. Peak withdrawal features may emerge 4–24 weeks after last 300 mg dose or 4–12 weeks after last 100 mg dose (CS).
Key adverse events	Systemic BPN adverse events	Systemic BPN adverse events Local injection site • Redness, pain, tenderness, swelling in approximately 5–10% patients. • Usually mild and transient and resolves spontaneously	As for Buvidal Weekly and Monthly

Regulatory requirements

Practitioners must obtain a permit from the Department of Health and Human Services before prescribing methadone, sublingual buprenorphine or buprenorphine/naloxone or long-acting injectable buprenorphine.

For the restricted registration period, the permit application for long-acting injectable opioid agonist therapy is a separate application form for long-acting injectable buprenorphine, with a note indicating it is only available to approved prescribers who have completed the administration training. Once the application is lodged, the permit received can be used for long-acting or sublingual buprenorphine.

The prescribing medical practitioner must record in the patient's file a record of prescription, including the patient's name and address, date of prescribing and date of administration, and the drug name (including the brand name), strength and the interval in which the injections are to be administered.

Currently, a permit is not required for the administration of long-acting injectable buprenorphine where a patient is a hospital inpatient or being treated in a hospital emergency department, for the time in hospital plus seven days after discharge. If long-acting injectable buprenorphine is administered in this context, it is strongly recommended that a permit application is made, to ensure there is a record of treatment for the individual. Note that long-acting injectable buprenorphine will not be captured on SafeScript as it will not be dispensed by pharmacies, therefore the permit will be the sole means of indicating that the patient may have been administered long-acting injectable buprenorphine.

Getting support and more information

Policy for maintenance pharmacotherapy for opioid dependence – summary of changes related to the use of long-acting injectable buprenorphine for opioid use dependence, April 2019 <https://www2.health.vic.gov.au/public-health/drugs-and-poisons/pharmacotherapy>.

National Guidelines for Medication-Assisted Treatment of Opioid Dependence (MATOD) <https://www.health.gov.au/resources/publications/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence>

Drug and Alcohol Consultant Advisory Service (DACAS) <https://www.dacas.org.au/>

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

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

Sublocade product information Australia <www2.health.vic.gov.au/public-health/drugs-and-poisons>

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