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

For Western Australian CPOP prescribers

November 2020

GOVERNMENT OF WESTERN AUSTRALIA

Department of Health
Mental Health Commission

Acknowledgements

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NSW guidelines prepared by Prof Nicholas Lintzeris, Prof Adrian Dunlop and Debbie Masters for NSW Health (2019).

SA brief clinical guidelines prepared by Professor Mike McDonough, Dr Chris Holmwood and Jane Scarborough for Drug and Alcohol Services South Australia (DASSA) (2020).

Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. Lintzeris N, Dunlop A, Masters D. (2019) NSW Ministry of Health, Sydney Australia.

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ACRONYMS

AE	Adverse Event
BPN	Buprenorphine
CAS	CPOP Advice and Support
CPOP	Community Program for Opioid Pharmacotherapy
CPOP CRC	CPOP Clinical Review Committee
CPP	Community Pharmacotherapy Program
DACAS	Drug and Alcohol Clinical Advisory Service
DDI	Drug-Drug Interaction
HDWA	Western Australian Department of Health (the Department)
MATOD	Medication Assisted Treatment of Opioid Dependence
MPRB	Medicines and Poisons Regulations Branch
OST	Opioid Substitution Treatment
SL	Sublingual

Introduction

These Western Australian Clinical Guidelines have been adapted with permission from The New South Wales brief clinical guidelines for the use of long-acting injected depot buprenorphine (depot BPN)[1] and the South Australian brief clinical guidelines[2].

This document contains information that is specific to the Western Australian CPOP and reflects current policy and procedures. The *Western Australian Clinical Policies and Procedures for the Use of Methadone and Buprenorphine in the Treatment of Opioid dependence* (the Manual) outlines the general principles of this and other substitution treatments available in WA. Prescribers of depot BPN should also be aware of the *Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence* (2019) NSW Ministry of Health, Sydney Australia.

This guideline has been developed to assist decision-making by clinicians and clients in the use of the depot BPN preparations and should be used in conjunction with the full Product Information, Consumer Information materials and demonstration videos provided by each depot BPN manufacturer.

It is important to understand that clinical guidelines are intended to guide clinical decision-making and practice and do not address every conceivable situation or exceptional circumstance. These guidelines may be updated with further clinical experience with use of depot in Western Australia.

In exercising good clinical judgement, it may be prudent to obtain additional assistance with decision-making and practice support. Such advice may be sought from:

- The Community Pharmacotherapy Program (CPP) Phone: 92191913
- CPOP Advice & Support (CAS) Phone 94425042
- CPOP Clinical Review Committee (consultation)
- Referral to an addiction specialist service could also be considered.

If clinical practice outside of recommendations is considered necessary, CPOP CRC endorsement of the treatment plan will be required. The reasons for, together with risk mitigation measures and the patient's informed consent should be documented as part of the patient's treatment plan and forwarded to the CPOP Clinical Review Committee.

Patient Selection

Patients appropriate to be prescribed depot BPN.

It is recommended that treatment initiation with depot buprenorphine is most appropriate for patients already undergoing treatment with buprenorphine (e.g. stable on a Suboxone or Subutex program). This ensures a patient's tolerance to buprenorphine before exposing them to long acting depot BPN products.

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[1] Lintzeris N, Dunlop A, Masters D (2019) Brief Clinical guidelines for use of depotbuprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia.

[2] McDonough M (2020) Brief Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia.

Recommended Indications:

- Opioid Dependence (currently on buprenorphine)
- Stability on OST e.g. on multiple take-away doses.
- Facilitates treatment goals e.g. maintaining employment, cost savings.

Special Precautions:

- Drug-drug interactions e.g. CYP3A4 Inhibitors and Inducers, Serotonergic Drugs, QTc,
- Respiratory depression and obstructive sleep apnoea syndrome (OSAS)
- Cardiac arrhythmias
- Severe renal impairment
- Pregnancy (Sublocade)
- Unstable ongoing drug use
- Moderate hepatic disease e.g. Child Pugh Class B

Contraindications:

- Allergy/sensitivity to buprenorphine (or depot excipients).
- Severe hepatic disease e.g. Child Pugh Class C
- Clients less than 18 years of age (Sublocade)
- Clients less than 16 years of age (Buvidal)
- Severe respiratory insufficiency
- Pregnancy and lactation (Buvidal).
- Acute alcoholism or delirium tremens

Refer to Product Information document (PI) for more detailed information.

Special warnings and precautions for use

Sublocade®

Risk of serious harm or death with intravenous administration.

Intravenous injection presents significant risk of serious harm or death as Sublocade forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously.

***Do not administer intravenously or intramuscularly.**

Buvidal®

Risk of Serious Harm or Death with Intravenous Administration

Serious harm or death could result if administered intravenously. Buvidal® Weekly and Buvidal® Monthly forms a gel depot upon contact with body fluids and may cause occlusion, local tissue damage and thromboembolic events, including life threatening pulmonary emboli, if administered intravenously.

***Do not administer intravenously or intramuscularly.**

Regulatory requirements

Depot BPN is a Schedule 8 drug, regulated in Western Australia by the Schedule 8 Medicines Prescribing Code and monitored by WA Health's Medicines and Poisons Regulation Branch (MPRB).

In Western Australia, a prescriber of BPN must be appropriately trained to be authorised by the Department of Health CEO to prescribe methadone and buprenorphine for the treatment of opioid dependence. Medical practitioners prescribing depot BPN must have undertaken additional training with successful completion of a face-to-face or online training and assessment package delivered by the Community Pharmacotherapy Program (CPP). They must also agree to comply with the conditions of the WA Clinical Policies and Procedures for the use of Methadone and Buprenorphine in the Treatment of Opioid Dependence and receive endorsement from the Director of Clinical Services at Next Step.

Additionally, the authorised prescriber must obtain an individual patient authority from the Department before prescribing methadone or buprenorphine to a drug dependent person.

Training to become an authorised prescriber of depot buprenorphine in the WA CPOP can be found on-line or may be provided face-to-face. For further information, call the Coordinator, Provider Support on 92191896 to discuss current options. Conditions for authorisation will be compliant with the WA CPOP as described in the CPOP Manual.

All patients commencing treatment with depot BPN injections must be eligible for OST under the current approved WA Policies and Procedures.

Depot BPN is indicated under the PBS S100 scheme for treatment of opiate dependence. The Australian Government funds the cost of this medication supplied as pharmaceutical benefits through clinics and pharmacies approved by State and Territory governments.

Buvidal® and Sublocade® medications must not be handled by, be accessible to, or dispensed DIRECTLY to patients or carers. All steps should be taken to avoid any possibility of diversion of depot injection/s to unauthorised persons. Buvidal® and Sublocade® must be administered by registered health practitioners. Serious harm or death could result if administered intravenously.

Access to Depot Buprenorphine

Arrangements will be needed to obtain the depot BPN product from an approved pharmacy. To be available to be administered to the patient by the health practitioner the product must be delivered to the prescriber's medical practice for administration. The dispensing, delivery, administration and any other movement of depot BPN must be recorded in an approved S8 Register, available from the preferred wholesaler.

- Cold chain storage principles must be maintained when transporting Sublocade® from the dispensing pharmacy to a medical practice.

Deliveries of depot BPN must be handed directly to an authorised health professional (pharmacist, medical practitioner or registered nurse) with appropriate recording of date, name and signature of receiver on the delivery receipt.

Original CPOP prescriptions must be provided to the pharmacist or their agent upon delivery to a medical centre.

Entries in the register must be completed and countersigned (when required) by an authorised health professional (pharmacist, medical practitioner or registered nurse).

All other record keeping requirements apply in full, including retention of signed delivery receipt.
All depot BPN scripts must comply with the following requirements

- HDWA Authorisation number
- Name of patient and current address
- Pharmacy supplying the depot and name of the practice for delivery
- Name of the medication (if Buvidal specify Weekly or Monthly)
- Dose (no date range required)
- Prescriber's name, signature and prescriber number
- Date of prescription
- No repeats allowed

All depot BPN products, such as doses awaiting administration to patients, must be stored in an appropriate safe, as defined in the Medicines and Poisons Regulations 2016.

Sublocade® is approved for storage at room temperature for up to 7 days and can therefore be stored in a safe at medical practices. Information about safes for medical practices is available on the Department website: https://ww2.health.wa.gov.au/Articles/S_T/Storage-of-Schedule-8-medicines

Pharmacies will require evidence of secure refrigerated storage before approval to supply Sublocade® will be provided.

Refer to the Department of Health's *Depot buprenorphine long-acting subcutaneous injections (Buvidal® and Sublocade®): Guidance note for pharmacists and medical practices* for information regarding requirements for refrigerated storage.

Depot buprenorphine products: Buvidal® and Sublocade®

The Clinical Guideline has been developed to inform decision-making by clinicians and clients in the use of the following long-acting injected depot buprenorphine (depot BPN) preparations, Buvidal® and Sublocade®.

Buvidal® (manufactured by Camurus) 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'. This product 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® (manufactured by Indivior) 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

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

Clinical tasks include:

- Reviewing medication doses
- Checking for adverse events
- Assessment of comorbidities
- Establishing therapeutic rapport
- Formulation of recovery plan
- Encouraging and facilitating access to psychosocial support.

Treatment with depot BPN potentially challenges the way in which OST services are structured and delivered. The less frequent dosing with depot BPN formulations may require a different approach to structuring clinical reviews, psychosocial interventions and treatment care planning.

Options:

- Consider weekly depot when commencing treatment for first 2-4 weeks
- Consider weekly depot for patients requiring more frequent monitoring (e.g. unstable psychiatric and social conditions)
- Monthly formulation – schedule more frequent clinical reviews, e.g. after initiation and during periods of instability

These issues should be discussed with individual clients when considering the choice of depot versus SL BPN treatment, and when developing treatment plans with clients. It should be emphasised that safe and effective OST is more than the provision of medication, and that regular reviews, treatment planning, and psychosocial interventions are important elements of OST and recovery.

There is minimal research evidence to guide choice between the depot formulations and SL BPN. Individual patient and clinician factors should be considered.

It is essential that patients are provided 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 remove 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 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. These options should remain available.

Buvidal® and Sublocade® must be administered by registered health practitioners.

Buvidal® and Sublocade® medications must not be handled by or dispensed DIRECTLY to patients or carers. Serious harm or death could result if administered intravenously.

Delivering treatment with depot BPN

The key characteristics of Buvidal and Sublocade and recommended dosing regimens are summarised in Table 2. Specific recommendations regarding medication regimens for each product are described below. Refer to the full guidelines (NSW) 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. It is not recommended to temporarily substitute one product with another.

Dosing recommendation for Buvidal®

Transferring from SL BPN.

Patients should be treated with ≥7 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 1 below.

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	8mg	No monthly equivalent
8-10mg	16mg	64mg
12-16mg	24mg	96mg
18-32mg	32mg	128mg

Patients should be reviewed before 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®.

Direct initiation of Buvidal® from short acting opioids (e.g. heroin, morphine, oxycodone, fentanyl) is not recommended. An initial period of sublingual BPN of ≥7 days is required prior to commencement of Buvidal®.

If there is a clinical indication for a shorter period of sublingual BPN (i.e. <7 days), a treatment plan must be submitted with the application for consideration by the CPOP CRC.

Flexible dosing schedule.

Patients may switch between Buvidal® Weekly and Buvidal® Monthly (see Table 1). Individual dose adjustment may be required.

- Buvidal® Weekly doses may be given up to 2 days before or after the weekly time point (days 5-9),
- Buvidal® Monthly may be given 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 possible. A re-induction to SL BPN may be required if >14 days has elapsed between Buvidal® Weekly doses, or >8 weeks between Monthly doses.

Supplemental or 'top up' BPN doses.

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

Comprehensive discussion and counselling regarding expected timeframes to reaching steady state may assist patients during the first few months of treatment in continuing with the chosen formulation.

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 128mg. If supplemental Buvidal® Weekly doses cannot be administered, supplemental doses of SL BPN (8mg daily) may be used for a limited period until the next depot injection can be organised. However, this will require a new HDWA authorisation for SL BPN, if the previous authorisation has expired. (Note: the SL BPN authorisation is generally maintained as valid for a period of one month following commencement of Buvidal®. The onus is on the prescriber to check the expiry date of the authorisation and submit a new application for SL BPN if necessary.

Buvidal® and pregnancy

Buvidal® is contraindicated in pregnancy and lactation. Therefore, patients should be advised of other options, provided special precautionary information and informed consent obtained before prescribing to women planning pregnancy or who are already pregnant. As with any medication use in pregnancy, use of Buvidal® depot BPN could be considered for continued use only if the potential benefit justifies the potential risks to the mother and baby. The CPOP CRC must be consulted if depot BPN continuation is to be considered during pregnancy. Key points to consider include:

- Patients should be involved in decision making regarding their treatment.
- Opiate agonist treatment is first line treatment for opiate dependence during pregnancy.
- Optimal ante-natal care for pregnant women who are on opiate agonist treatment includes regular liaison between their opiate treatment team and the ante-natal care team.
- A neonatal opioid withdrawal syndrome is considered likely to occur if continued late in pregnancy as has been reported with the sublingual formulations.

Discontinuing Buvidal

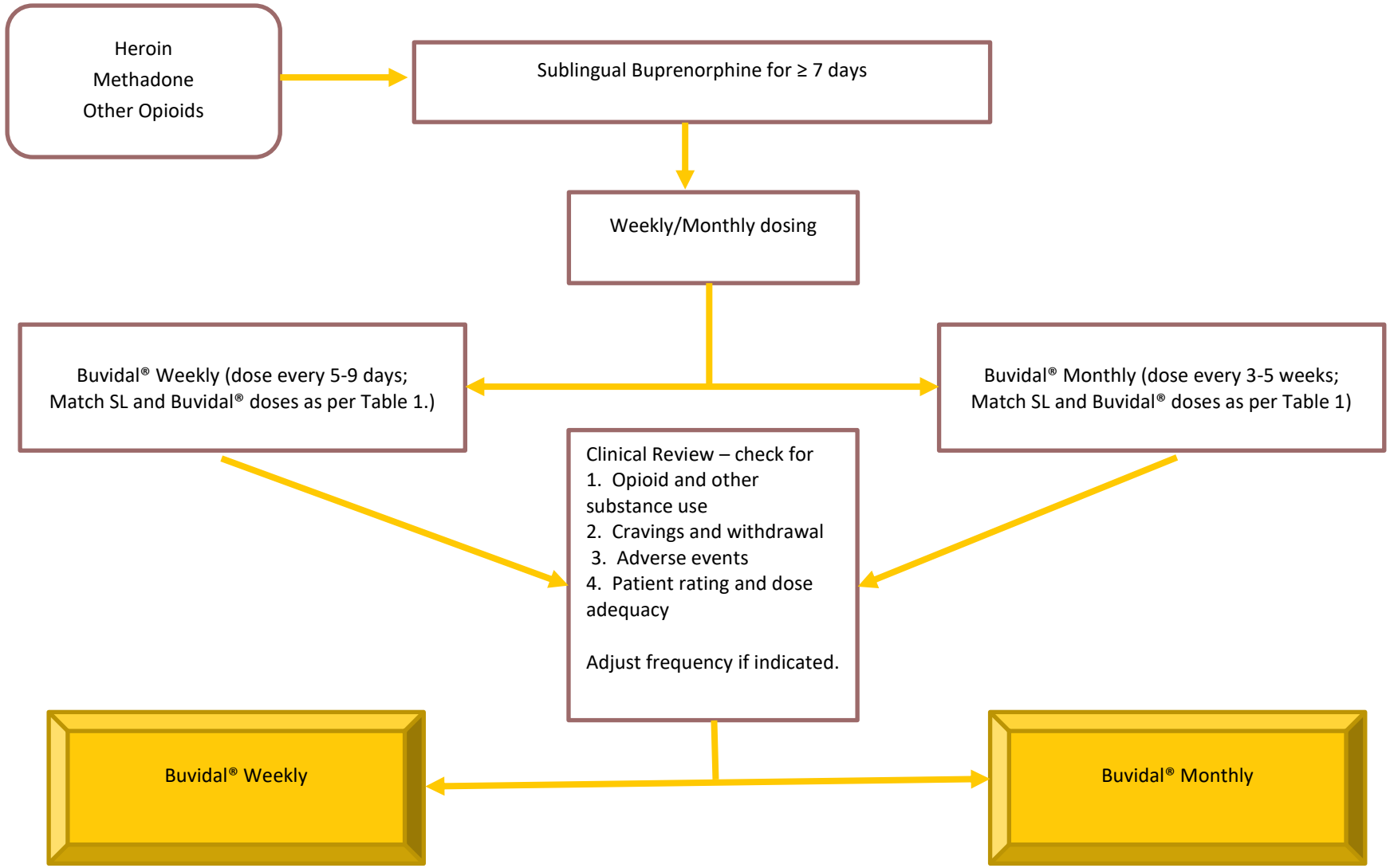
Currently, no studies have been performed to examine discontinuation of Buvidal®. It may have a duration of effect lasting longer than the anticipated effect of the Weekly or Monthly depot injection, especially after prolonged use and with steady-state blood levels achieved. Therefore, withdrawal symptoms and signs may be delayed for days to weeks. Withdrawal is likely to emerge within 1 to 4 weeks following regular dosing with the Weekly depot or 4 – 12 weeks following the Monthly depot injection.

There are multiple dose formulations of Buvidal® so a slow reducing titration can be provided by using successively lower dose depot injections. At the end of such a discontinuation procedure, some patients may still require continued buprenorphine weaning with transfer to sublingual Suboxone®/Subutex®. It is good practice to document why a patient (or you) has decided to discontinue treatment and to always provide relapse prevention education together with follow up support and access to naloxone (e.g. Nyxoid nasal spray or Prenoxad® Solution for Injection).

Transferring from 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 and titration of the SL dose over subsequent days.

Figure 1: Overview dosing with Buvidal



Dosing recommendations with Sublocade®

Commencing Sublocade® treatment.

Sublocade® treatment requires preceding treatment with SL BPN for at least 7 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 300mg dose each month for the first 2 months, providing 'loading' doses that elevate plasma BPN levels more rapidly during the initial treatment period.

Sublocade® may be initiated with 100mg doses where there may be safety concerns relating to high BPN plasma levels (e.g. severe hepatic disease, DDIs). Induction at lower doses is considered "off-label" and the CPOP CRC should be contacted for advice.

Following the initial two monthly Sublocade® 300mg doses, for most patients 100mg Sublocade® maintenance doses every 4 weeks thereafter will be adequate for maintaining plasma levels at steady state equilibrium.

300mg monthly doses may be considered thereafter for those patients who had previously stabilised on high dose SL BPN (e.g. 24mg daily) or who continue to experience cravings, withdrawal or unsanctioned opioid use during the first 2-month period of Sublocade® dosing. This dosing regimen may also be considered for patients who continue to experience cravings, withdrawal or unsanctioned opioid use whilst receiving maintenance 100mg Sublocade® doses.

Sublocade® flexible dosing schedules.

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.

If a dose is missed, the next Sublocade® dose should be administered as soon as practically possible. Re-induction via SL BPN pathway may be required if more than eight weeks between Sublocade® doses has elapsed. Prescribers can contact CPP or CAS for advice as a new HDWA authorisation for SL BPN will be required.

Discontinuing Sublocade.

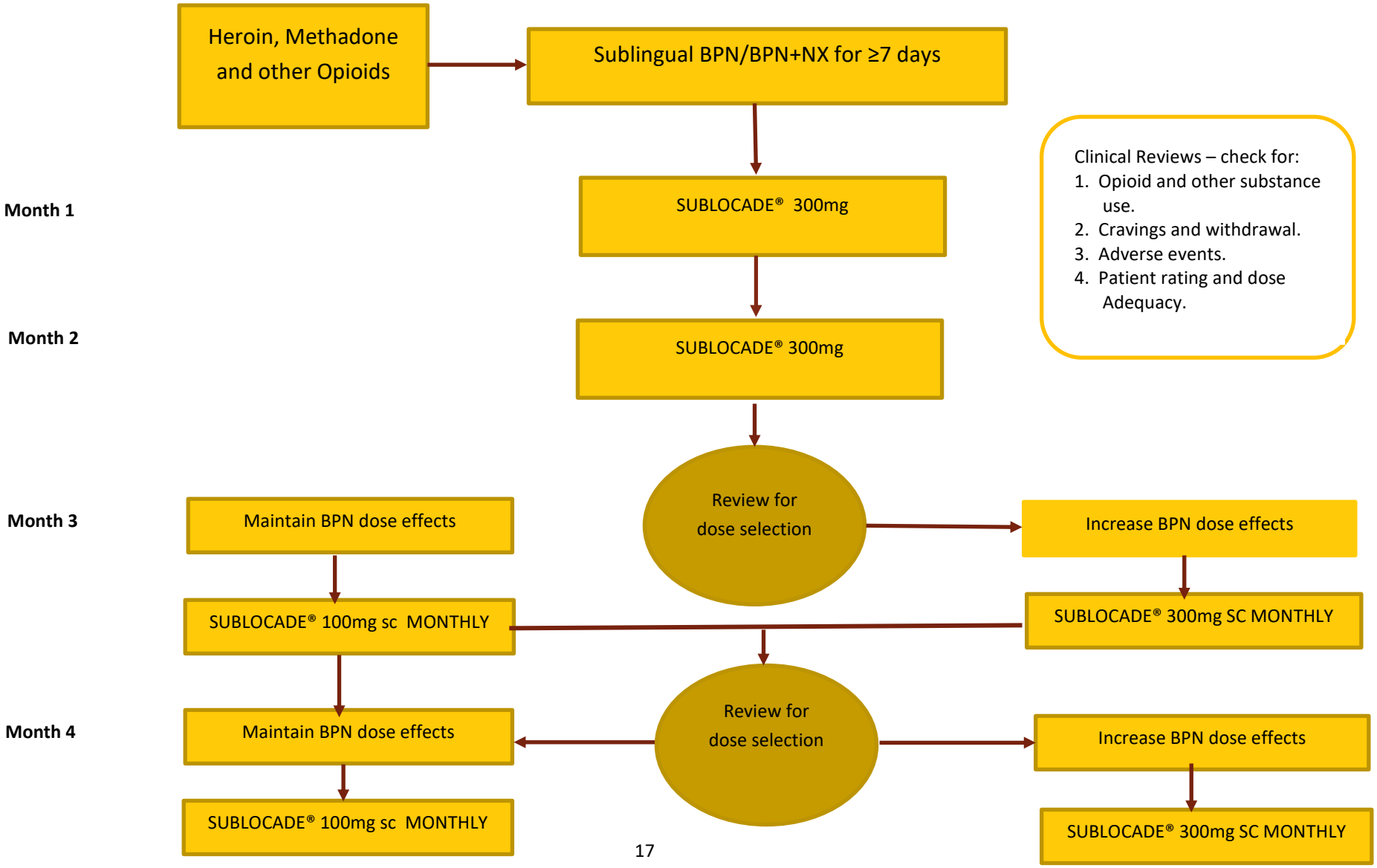
Sublocade ® may last significantly longer than the month for which the different formulations are designed. Peak withdrawal features may emerge 4-24 weeks after last 300mg dose or 4- 12 weeks after last 100mg dose. If a slow dose taper is desired, then titrate down the Sublocade® dose as tolerated. Monitor for withdrawal. SL preparations might need to be considered in addition to, or as a substitute for, the Sublocade ®. If sublingual dosing is considered necessary, a new application is required. It is good practise to document why a patient (or you) has decided to discontinue treatment and to always provide relapse prevention education and follow up together with access to naloxone (e.g. Nyxoid or Prenoxad)

Transferring from Sublocade® to SL BPN

Recommended practice is to initiate SL BPN with low doses at approximately the time of the next scheduled depot BPN injection – usually commencing with 8mg SL BPN four weeks after the last Sublocade® dose, and to titrate the dose upwards over subsequent days or weeks according to clinical need as the depot BPN concentrations gradually subside, aiming to achieve the expected SL dose based on

clinical assessment and patient report. Frequent clinical reviews are recommended. CPP or CAS can be contacted for advice.

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 (e.g. alcohol, benzodiazepines), severe hepatic disease, pregnancy and lactation, cardiac arrhythmias, and respiratory depression (see Product Information for details).

Adverse events (AEs).

Depot products can be associated with local injection site AEs – redness, pain, tenderness and swelling in 5-10% 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 (e.g. 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 concerns, stabilise on SL BPN and monitor DDI before transferring to depot BPN products.

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 required for a minimum of 1-2 weeks prior to commencing depot treatment.

Transfer to methadone

Since there are no published studies and little clinical experience, patients seeking to transfer from depot BPN to methadone should transition via SL BPN. Once stabilised on a dose of SL BPN for at least 2 weeks, transition to methadone can occur initiating at low doses (20-25mg) daily with regular review and careful titration of doses. An Addiction Medicine Specialist should be consulted.

Transferring between depot products

Currently there are no studies to provide evidence about transferring between BPN products. There are very limited anecdotal reports of transfer between BPN products and while this can be done if necessary, it should proceed with caution.

The prolonged duration of effect with both depot products and especially Sublocade® 300mg, would generally require delaying transfer until the withdrawal process can be reasonably established following which induction onto the other depot could commence. In some circumstances the new depot BPN injection may not be available at a time when withdrawal has commenced, in which case the patient may be temporarily provided SL BPN to manage withdrawal until the new depot BPN can be initiated. CPP should be contacted for assistance in these circumstances as a new HDWA authorisation for SL formulation will/may be required.

It is recommended that referral to an Addiction Medicine Specialist be undertaken for a patient seeking transfer between depot BPN products or conferring with a specialist about proposed management.

Pregnancy and breastfeeding.

Buvidal® is contraindicated for use in pregnancy and lactation. The Product Information for use of Sublocade® in pregnancy and lactation recommends precautionary use.

While 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. The CPOP Clinical Review Committee must be consulted regarding continuation of depot products to pregnant or breastfeeding women.

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 until the prescriber and patient are satisfied that depot BPN does not adversely affect their ability to engage in such activities. People on a stable dose may not be at higher risk, providing the dose has been stabilised over some months and they are not using other impairing drugs.

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 4-12 weeks after last Buvidal® Monthly dose, or 1-4 weeks after last Buvidal® Weekly dose. For Sublocade® peak withdrawal features may emerge 4- 24 weeks after last 300mg dose or 4-12 weeks after last 100mg dose. Withdrawal symptoms may persist for weeks (or months) and are expected to be less severe than withdrawal from shorter- acting opioids. Although 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 health care professional and must never be dispensed or supplied directly to the patient or carer.

Special populations, treatment settings and clinical scenarios.

The use of depot BPN products in certain patient populations and treatment settings (correctional facilities, hospitals, residential rehabilitation), and in the management of clinical scenarios (acute and chronic pain management, overdose, intoxicated presentations) is described in the *Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence (2019).* Centre for Alcohol and Other Drugs. NSW

Table 2. Overview of buprenorphine products available for treatment of opioid dependence in Australia.

	SL Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Formulations	Suboxone® contains buprenorphine (BPN) and naloxone in 4:1 ratio 2/0.5mg and 8/2mg sublingual film Subutex® contains buprenorphine in 0.4mg, 2mg and 8mg sublingual tablets	Buvidal® Weekly and Monthly contain BPN in FluidCrystal® injection depot technology Subcutaneous (SC) injections in prefilled syringes with 23 gauge needle. Administration via upper arm, thigh, abdomen or buttocks Buvidal® Weekly: 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL; 32mg/0.64mL Buvidal® Monthly: 64mg/0.18 mL, 96mg/0.27 mL; 128/0.36 mL	Sublocade® contains BPN in the ATRIGEL® Delivery System SC injections in prefilled syringes with 19 gauge needle administered in abdomen Monthly doses: 100mg/0.5mL or 300mg/1.5mL
Storage requirements	Store at room temperature (below 30°C)	Store at room temperature (below 25°C). Do not refrigerate or freeze.	Cold storage requirements (2-8°C). May be stored at room temperature (below 25°C) for up to 7 days before use. Remove from cold storage for at least 15 minutes prior to SC injection.
Clinical pharmacology	Bioavailability 10-30% Onset effects within 1 hour, with peak effects 2-4 hours after dose Duration effects usually 24 hours but dose dependent and can vary from 8 to 72 hours	Bioavailability = 100% Time to peak plasma level (Tmax) • 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 (Tmax) = 24hrs Half life = 43 to 0 days Steady-state equilibrium by 2nd (300/100mg) to 6th dose (300/300mg)

Frequency of dosing	Daily, two or three day doses. Take-aways and unsupervised dosing available for low risk	Buvidal® Weekly dose can be administered every 7±2 days (5-9 day schedule) Buvidal® Monthly dose can be administered every 4±1 weeks (3-5 week schedule)	Sublocade® dosed every 4 weeks (26-42 day schedule)
Key Drug – Drug Interactions (DDIs)	Systemic BPN DDI include: – Opioids agonists: can reduce effects other opioids (blockade); BPN may precipitate withdrawal on induction – Sedatives (e.g. benzodiazepines, alcohol, TCAs, antipsychotics, gabapentinoids): sedation, respiratory depression, overdose A number of potential DDI can occur but are rarely of clinical significance (e.g. interactions with medications that induce or inhibit CYP450 and can lower or increase BPN plasma levels); or are rare (e.g. serotonergic syndrome in combination with medication such as SSRIs, MAOIs, tramadol; or medications that can cause QT prolongation and increase 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.		
	SL Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Recommended dosing regimen Commencing treatment	From heroin, morphine: Commence 8mg Day 1 when patient in early / mild opioid withdrawal (usually >8-12hrs 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: initial dose of 2mg, followed by an additional dose of 4 - 6mg after 1-2 hrs, if	Buvidal® dose should be determined according to patient's SL BPN dose (see Table 1). Titrate subsequent doses after clinical review. Note increasing effects during first few doses (accumulation to steady state after about 4 doses) Note: Direct initiation of Buvidal® from short acting opioids (e.g. heroin, morphine, oxycodone, fentanyl) will not be supported.	Initiate treatment with SL BPN (minimum dose 8mg) for 7 days, then transfer to Sublocade®. Recommended induction: Months1 and 2: 300mg monthly injections Month 3 onwards: 100mg monthly doses (if patient 'stable' on initial 2 x 300mg doses) or 300mg monthly doses if requiring additional BPN effects (e.g. cravings, withdrawal, continued opioid use).

	there is no precipitated withdrawal with the initial dose. Day 2 onwards: titrate BPN dose daily as required.	An initial period of SL BPN of ≥7 days is required prior to commencement of Buvidal®. If there is a clinical indication for a shorter period of SL BPN (i.e. <7 days), CPOP CRC must be consulted.	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 (<8mg) and referral to CPOP CRC for advice and support is required. 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 - 24mg daily (32mg 2nd or 3rd 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 to months (e.g. 2-4mg 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.	Reduce dose to 100mg monthly injections prior to stopping. Peak withdrawal features may emerge 4-24 weeks after last 300mg dose or 4-12 weeks after last 100mg dose.
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	

Other issues

Accessing depot BPN supplies and storage considerations

Buvidal® and Sublocade® medications should not be handled by, be accessible to, or be dispensed DIRECTLY to patients or carers. All steps should be taken to avoid any possibility of diversion of depot injection/s to unauthorised persons. Buvidal® and Sublocade® must be administered by registered health practitioners. Serious harm or death could result if administered intravenously.

Each prescriber of depot BPN will need to arrange for the supply of this product to be available for administration to the patient. Individual pharmacies will need to be contacted in this regard and will be required to be authorised by the WA Department of Health prior to engaging in the ordering and dispensing of depot BPN products.

A fee structure and method of payment by the patient for any cost for the supply of the medication will need to be determined with the pharmacy and communicated with the patient as part of the treatment plan. Most patients will be charged a service and delivery fee with payment made prior to dosing.

There are also storage considerations for depot BPN products.

- Buvidal® is stable at room temperature and can be stored for up to 2 years.
- Sublocade® requires refrigeration in an S8 compliant fridge in pharmacies where it can be stored for up to two years. Sublocade® can be stored in a compliant drug safe for a maximum of one week at room temperature in medical practices after which time it must be returned to the pharmacy.
- The size of the packaging should be considered to ensure that there is capacity to store the medication in a compliant manner.

Record Keeping

The prescriber must indicate in the patient's file a record of prescription, including:

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

Along with the usual Informed Consent process required for medical treatment, the prescribing medical practitioner should provide an alert card for patients (provided with the product or from the manufacturer) and specific printed depot BPN information, available online and from the manufacturer.

Monitoring Treatment.

The requirements for clinical monitoring of patients maintained on depot BPN are similar to when oral formulations are used for OST. The use of depot BPN removes the need to determine take away doses or to monitor pharmacy attendances. Appropriate clinical monitoring is outlined in the CPOPClinical Policies and Procedures for the use of methadone and buprenorphine int the treatment of Opioid Dependence.

Clinical review provides an opportunity to assess:

- The patient's general presentation, the quantity and frequency of any substance use since the last review, general health and wellbeing, social circumstances, living environment and relevant risk factors (child protection, harm to self or others, domestic violence, overdose, blood-borne virus risk);
- The current medication conditions, adequacy of medication dose, side effects, frequency of reviews, monitoring and counselling services; and
- Treatment progress against the treatment plan.

Urine Drug Screening (UDS)

UDS should be undertaken to monitor for other drug use.

Getting support & more information

Community Pharmacotherapy Program (CPP)	Tel: 92191913

The following numbers are for health professionals only and should not be given to patients.

CPOP Advice and Support (CAS)	Tel: 9442 5042
Drug and Alcohol Clinical Advisory Service (DACAS)	Tel: 6553 0520
Medicines and Poisons Regulation Branch (MPRB)	1) Tel: 9222 6883 (main) or 2) Tel: 92226812 (CPOP specific)

Consumer and Product information

AUSTRALIAN PRODUCT INFORMATION
Buvidal® Monthly (buprenorphine)

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02611-1&d=202003221016933

Buvidal® Monthly Buprenorphine Consumer Medicine Information

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-CMI-01178- 1

AUSTRALIAN PRODUCT INFORMATION
Buvidal ®Weekly (buprenorphine)

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

Buvidal® Weekly Buprenorphine Consumer Medicine Information

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-CMI-01177- 1

AUSTRALIAN PRODUCT INFORMATION
Sublocade® (buprenorphine)

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01756- 1

Sublocade® Buprenorphine Consumer Medicine Information
https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-CMI-01182-1

Administration videos

- Buvidal® – Product demonstration online video

  https://buvidal.com.au/wp-content/uploads/2019/08/Buvidal-Administration-September_2019_1_2.mp4

- Sublocade® – Learn how to administer SUBLOCADE® online
  https://app.box.com/s/0s6ukizr69qw51j6vdwfhjtbaowmxgtl

Clinical guidelines

Western Australia. Community Program for Opioid Pharmacotherapy (CPOP). Clinical Policies and Procedures for the use of Methadone and Buprenorphine in the Treatment of Opioid Dependence

- https://www.mhc.wa.gov.au/media/1614/wa-clinical-policies-and-procedures-for-the-use-of-methadone.pdf

National Guidelines for Medication-Assisted Treatment of Opioid Dependence 2014

- https://www.health.gov.au/resources/publications/national-guidelines-for-medication-assisted-treatment-of- opioid-dependence

Depot buprenorphine long-acting subcutaneous injections (Buvidal® and Sublocade®). Guidance note for pharmacists and medical practices. (October 2020) Health Department of WA

- https://ww2.health.wa.gov.au/Articles/N_R/Opioid-substitution-treatment

Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

- https://www.health.nsw.gov.au/aod/Publications/full-depot-bupe-interim-gl.pdf