NSW Health

Long-acting injectable buprenorphine (LAIB) for opioid dependence treatment

Guidance document

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  - Camurus (manufacturers of Buvidal) and Indivior (manufacturers of Sublocade)
- Kevin Street, consumer advocate and member of the CAOD Consumer Reference Committee

Disclaimers

This document is a guide to recommended practice, to be used as a resource alongside clinician judgement and patient choice. The document is designed to provide information to assist decision-making and is based on the best available evidence at the time of development of this publication.

Contents

Background

This Guidance has been developed to inform clinicians prescribing and administering long-acting injectable buprenorphine (LAIB) preparations.

LAIB formulations currently registered in Australia are: Buvidal Weekly and Buvidal Monthly, manufactured by Camurus; and Sublocade, manufactured by Indivior. These products are available on the Pharmaceutical Benefits Scheme (PBS) under an s100 opioid-dependence listing.

This Guidance is an update of the first (interim) NSW *Clinical guidelines for use of depot buprenorphine (Buvidal and Sublocade) in the treatment of opioid dependence*, published in 2019 [1]. It incorporates clinical and consumer experience, research evidence, and updated product information for both LAIB formulations since the 2019 guideline.

This Guidance:

1. assumes that clinicians are experienced in managing patients with opioid dependence, and in using sublingual (SL) buprenorphine (BPN) formulations and methadone in the treatment of opioid dependence
2. is to be used in conjunction with the
    - NSW Clinical Guidelines: Treatment of Opioid Dependence – 2018[1] [2] (NSW OTP Guidelines hereafter)
    - National Guidelines for Medication-Assisted Treatment of Opioid Dependence 2014 [3]
3. complements other guides and guidelines from the specialist alcohol and other drugs (AOD) treatment sector, including but not limited to:
    - NSW Health Alcohol and Other Drugs Psychosocial Interventions: Practice Guide[2]
    - NADA Practice Guide: Providing Alcohol and Other Drug Treatment in a Residential Setting[3]
    - NSW Health Management of Withdrawal from Alcohol and other Drugs[4]
    - NSW Health Clinical Care Standards for Alcohol and Other Drug Treatment[5]
4. has been informed by a synthesis of:
    - published evidence for Buvidal Weekly, Buvidal Monthly (CAM 2038) and Sublocade (RBP-6000); studies are referenced throughout the document
    - updated product information for Buvidal Weekly, Buvidal Monthly and Sublocade (formulations registered in Australia with the Therapeutic Goods Administration [TGA])
    - treatment conditions and regulatory frameworks for the use of BPN in opioid dependence treatment (ODT) in NSW [2, 3]
    - clinical experience in using LAIB formulations in Australian clinical trials and practice
    - consensus expert opinion of clinicians and consumer representatives with experience of LAIB treatment, including the guidance working group formed by NSW Health.

Note: Some recommendations in this document are not included in the TGA Buvidal or Sublocade product registration and can be considered 'off-label' use. Healthcare professionals are encouraged to use their judgement and consider the most recent evidence in addition to referenced information. Updates to the NSW Clinical Guidelines: Treatment of Opioid Dependence are anticipated. Wherever guidance is provided that is not directly informed by research evidence, the document will highlight these sections as Consensus Statements (CS).

[1] www.health.nsw.gov.au/aod/Pages/nsw-clinical-guidelines-opioid.aspx

[2] www.health.nsw.gov.au/aod/resources/Pages/psychosocial-interventions.aspx

[3] nada.org.au/resources/providing-alcohol-and-other-drug-treatment-in-a-residential-setting/

[4] www.health.nsw.gov.au/aod/professionals/Pages/clinical-guidance.aspx

[5] www.health.nsw.gov.au/aod/Pages/clinical-care-standards-AOD

Language

Language should be used in ways that demonstrate respect for the agency, dignity and worth of all people. The terms person and people are used throughout this publication, alongside the term patient – denoting when a person becomes engaged by a treatment service that then has a duty of care to them.

Acronyms

ACDAN	Aboriginal Corporation Drug and Alcohol Network
ADARRN	Aboriginal Drug and Alcohol Residential Rehabilitation Network
AHPRA	Australian Health Practitioner Regulation Agency
AIHW	Australian Institute of Health and Welfare
AOD	alcohol and other drugs
BBV	blood borne virus
BPN	buprenorphine
BNX	buprenorphine-naloxone film
CALD	culturally and linguistically diverse
CAOD	Centre for Alcohol and Other Drugs
CMI	Consumer Medicines Information
CNS	central nervous system
CS	Consensus Statement
DFV	domestic and family violence
DDI	drug–drug interaction
EN	enrolled nurse
IM	intramuscular
IV	intravenous
LAIB	long-acting injectable buprenorphine
LGBTIQ+	lesbian, gay, bisexual, transgender, intersex, queer and other sexual and gender identities
LHD	local health district
MoH	NSW Ministry of Health
NADA	Network of Alcohol and other Drugs Agencies
NDARC	National Drug and Alcohol Research Centre
NGO	non-government organisation
NOWS	neonatal opioid withdrawal syndrome
NUAA	NSW Users and AIDS Association
NSAID	non-steroidal anti-inflammatory drug
NTX	naltrexone
NX	naloxone
ODT	opioid dependence treatment
OTAC	Opioid Treatment Accreditation Course
OTP	opioid treatment program (NSW)
PBS	Pharmaceutical Benefits Scheme
PSU	Pharmaceutical Services Unit
RCT	randomised control trial
RN	registered nurse
SC	subcutaneous (injection)
SL	sublingual
TCA	tricyclic antidepressant
TGA	Therapeutic Goods Administration (Australia)
THN	take home naloxone

Training

A range of free education opportunities are available for health professionals.

For medical and nurse practitioners, completion of the Fundamentals of Opioid Treatment and the Opioid Treatment Accreditation Course (OTAC) serve as the first two steps to applying for accreditation to prescribe opioid pharmacotherapies in NSW. Other activities provided are not required for accreditation.

See otac.org.au to access the opportunities below.

	Fundamentals of Opioid Treatment	Opioid Treatment Accreditation Course	Driving safety and opioid treatment	Long-acting injectable buprenorphine	Clinical case webinars
Duration	60 minutes	1 day	40 minutes	60 minutes	60 minutes
Required for accreditation	Yes	Yes	No	No	No
Delivery mode	Online (eLearning)	In-person or online (webinar + eLearning)	Online (eLearning)	Online (eLearning)	Online (live webinar)
Course summary	An introductory module for health professionals interested in learning more about core concepts of the NSW Opioid Treatment Program and the safe prescribing of opioid pharmacotherapies.	A comprehensive course on opioid treatment, facilitated by addiction medicine specialists. Aligning with the NSW Clinical Guidelines: Treatment of Opioid Dependence, the OTAC allows medical and nurse practitioners to become an accredited prescriber of opioid pharmacotherapies in NSW.	Explore the potential impact of treatments and other factors on driving safety. Plus learn about short and long-term fitness to drive, with a focus on sedating medications and opioid dependence treatment.	This short course is designed to support prescribers and other health professionals in NSW in providing this treatment in a safe and effective manner.	Interactive webinars to provide health professionals with a continuing learning environment to discuss clinical matters related to prescribing methadone or BPN pharmacotherapies for opioid dependence. Sessions include case-based discussions and relevant topic resources.

Training for pharmacists

Specific accredited training is recommended for pharmacists providing LAIB. It is available via the Pharmaceutical Society of Australia.[6]

[6] https://my.psa.org.au/s/training-plan/a110o00000KYp5HAAT/nsw-longacting-injectable-BPN-administration-by-pharmacists

Resources for patients

NSW Users and AIDS Association (NUAA) resources	
General resource page	https://nuaa.org.au/resources
Consumer guide to opioid treatment programs (OTPs)	https://nuaa.org.au/opioid-treatment-programs

Consumer Medicines Information (CMI) for opioid dependence treatments (ODTs)		
Drug	**Route of administration**	**Link to CMI** All CMIs are available at https://www.nps.org.au/medicine-finder
Buprenorphine	Subcutaneous injection (long acting)	Sublocade Buvidal Weekly Buvidal Monthly
Buprenorphine	Sublingual	Subutex
Buprenorphine and Naloxone	Sublingual	Suboxone Film
Methadone	Oral	Aspen Methadone Syrup Biodone Forte
Naltrexone	Oral	Naltrexone GH

Take home naloxone (THN)		
NSW Health – Your Room website	Information about THN, including where to obtain free THN	https://yourroom.health.nsw.gov.au/getting-help/Pages/Naloxone.aspx
NSW Health Opioid Overdose Response fact sheets	Nyxoid	https://www.health.nsw.gov.au/aod/programs/Factsheets/naloxone-factsheet-nyxoid.PDF
	Prenoxad	https://www.health.nsw.gov.au/aod/programs/Factsheets/naloxone-factsheet-prenoxad.PDF

Participating community pharmacies	
Map of community pharmacies that supply LAIB	https://www.health.nsw.gov.au/aod/Pages/opiod-treatment-map.aspx

1. Opioid dependence treatment (ODT) with LAIB medications

1.1 An overview of LAIB for ODT

The introduction of LAIB in Australia has been a significant development, representing an additional treatment option for those on ODT and offering a reduction in the restrictions associated with medications designed to be administered daily (or at intervals of up to three days for a small proportion treated with sublingual [SL] BPN).

Clinical studies have demonstrated enhanced outcomes with LAIB compared to placebo and SL BPN treatment [4–10], most notably with regards to treatment outcomes, patient experience and cost effectiveness.

LAIB may be the preferred medication for many; however, it will not suit all patients on ODT. Some patients will prefer SL BPN or methadone treatment, and these options should be made available, where possible. It is essential that patients are provided accurate information and options regarding their treatment, as part of informed decision-making and consent. Patients should be given a choice (where possible) of the type of LAIB they are prescribed.

Regardless of setting, all ODTs should be delivered according to the principles of person-centred care, as outlined in Clinical Care Standards: Alcohol and Other Drug Treatment,[7] including:

- treating patients with dignity and respect
- encouraging and supporting patient participation in decision-making
- communicating and sharing information with patients about clinical conditions and treatment options
- providing patients with information in a format that they understand so they can participate in decision-making.

[7] www.health.nsw.gov.au/aod/Pages/clinical-care-standards-AOD.aspx

ODT with methadone or BPN has been demonstrated to be a safe and effective approach for addressing opioid dependence, which can provide the opportunity to engage patients with other health and psychosocial interventions. The key elements of ODT are:

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

Treatment approaches for ODT are covered extensively in the NSW OTP Guidelines.[8]

1.1.1 LAIB treatment practice settings

LAIB 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.

Medical support may be provided by a medical practitioner (e.g. general practitioner, addiction medicine specialist, addiction psychiatrist, pain specialist) or a nurse practitioner with an addiction scope of practice.

Social and psychological support may be provided by medical, nursing and/or allied health staff (including AOD workers, pharmacists, counsellors, psychologists, social workers, consumer workers) and peer support services (e.g. Smart Recovery, 12-step programs) depending on patient needs and resources available.

Administration (injection) must be provided by suitably trained and credentialled healthcare providers (medical practitioners, nurses, pharmacists), and can be delivered in public or private clinic settings, community pharmacies, private medical practices, hospital settings, custodial settings and residential rehabilitation services. See Chapter 6: Administering LAIB injections, for more information.

Coordination and scheduling of ODT services. Patients taking LAIB may attend for medication less frequently and this may require a different approach from clinicians when structuring clinical reviews, psychosocial interventions, and in treatment care planning. Safe and effective ODT is more than the provision of medication. Regular reviews, treatment planning and psychosocial interventions are important elements of safe and effective ODT.

[8] www.health.nsw.gov.au/aod/Pages/nsw-clinical-guidelines-opioid.aspx

1.2 Evidence of efficacy of LAIB 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 randomised control trial (RCT) [8] on the primary endpoint of unprescribed opioid use; and demonstrated to be superior to SL BPN treatment on patient-reported outcomes of effectiveness, treatment convenience and global satisfaction [4]. An RCT of Sublocade (300/100 mg and 300/300 mg groups) demonstrated better treatment retention and significantly less unprescribed opioid use than the placebo group [9], with no apparent differences between the two Sublocade dosing regimens (300-100 mg compared to 300-300 mg dose conditions), although the 300-300 mg arm experienced more adverse events than the 300-100 mg group. One RCT has compared Sublocade to active treatment with SL BPN or oral methadone, demonstrating enhanced outcomes regarding the primary outcomes of heroin use and cost effectiveness [7].

1.3 Patients in focus

Patients in focus

This image (left) is used throughout the document to draw attention to information that patients have indicated is important to them.

This image is a prompt to always remember the person at the centre of ODT.

LAIB should always be presented as one choice in the range of currently available ODT medications.

Patients will need comprehensive information and reassurance from their clinicians as they assess whether LAIB will be compatible with their lifestyle and where they are in their treatment journey.

Clinician support will need to continue if they decide to transition to LAIB. No matter the advantages of the new mode of treatment, LAIB is a significant change for many patients. For some patients this may signify a reduction of autonomy, with less control over the timing of LAIB doses compared to daily medication.

Patients will respond differently to LAIB, with some satisfied with the treatment immediately and others needing more time to adjust or discontinue LAIB. There will be patients who wish to transition from SL BPN, as well as patients on methadone who will be interested in transitioning to LAIB. All patients will need to know how this ODT medication is similar to, or differs from, the formulation they are currently taking, and what is involved in the transition.

There are many patients who will find LAIB fits well with their treatment goals, but because they may have less contact with prescribers or dosing agencies, they may need support that is different from patients on other ODT medications.

The decision and transition should occur within a cooperative therapeutic relationship that balances a clinician's expertise and knowledge with a patient's treatment goals.

Patients in focus

Patients need to be equipped with adequate information about LAIB

Patients should be advised of the following information.

- The available LAIB treatment options and differences between the two medications. If only one option is offered, provide the rationale for this.
- The formulation pharmacology profile, effectiveness, duration of action and time of peak effects.
- Expected impacts on drug use, withdrawal and cravings.
- Prescribing and dosing procedures, including timing of medication options (weekly versus monthly), duration of effect and how administration routines occur.
- Possible safety issues, including side effects, overdose risks, interactions with alcohol and other drugs or medications, safety in pregnancy (and contraception options) and safe driving.
- Risks and features of opioid overdose, and how overdose can be prevented or managed (including access to THN).
- How transfer from other ODT medications can take place, and possible adverse events (e.g. withdrawal symptoms).
- Options for exiting the program, or transferring ODT to other service providers.
- Patient rights and responsibilities.
- Expected financial implications.

Champion agency and choice in your relationship with your patients.

- Recognise that LAIB will suit some but not all people currently on ODT.
- Listen to patients, take problems seriously and respond promptly to their descriptions, e.g. that the medication is not holding them, or that they are experiencing side effects.
- Listen to people's stories, goals, challenges and expectations about their treatment.
- Advise and guide your patient to assist them to choose the best medication fit for them.
- Encourage them to compile a list of advantages and disadvantages to help them with their decision-making.
- Offer a move to LAIB as a trial, reassuring them that they will be able to return to SL BPN or methadone liquid if LAIB does not suit them, and what the process entails.
- Respect your patient's decision to refuse LAIB even if you do not agree with their objections.
- Make sure the patient has sufficient harm reduction information, with special attention to overdose risks and reversal.

Set your patient up for success.

- Create a sense of psychological safety by actively listening to their concerns, avoid stigmatising language and judgement, respect their privacy and confidentiality, and be sensitive to their cultural and personal identity.
- Make clinical decisions that do not discriminate, punish, or reward but rather provide professional responses to any clinical challenges that might arise.

- Work collaboratively with your patient to prepare or review and amend their treatment plan and goals, including discussing reasons for missed or late doses, and expectations around exiting the program.
- Talk through options around treatment beyond medication issues (counselling, case management, peer support, etc.).
- Ensure key stages of treatment are discussed – treatment planning, monitoring and review, psychosocial and other support services, and discharge planning. Actively involve the patient and do so routinely.
- Ensure ongoing support and connection, especially if the patient is moving from very regular contact with a service providing ODT.
- Explain they should not drive or operate heavy machinery while they are getting used to the new formulation, or after a dose change, until their prescriber advises they can do so. Explore alternative transportation arrangements where necessary.
- Explore the patient's psychosocial wellbeing in the event that transition to LAIB disrupts their usual routines or coping mechanisms.
- Make sure patients have access to the *Consumers' Guide to the NSW Opioid Treatment Program* (published by NUAA online www.nuaa.org.au) and any of the several special consumer interest guides, including the guide to LAIB.
- Tell your patient about:

  PeerLine A confidential peer-run telephone service providing support to people who use drugs, who are on the OTP or who are seeking treatment across NSW. **1800 644 413** or email peerline@nuaa.org.au

  The Opioid Treatment Line (OTL) A telephone helpline that provides opioid pharmacotherapy information, referrals, advice and a forum for pharmacotherapy concerns. 9:30am to 5:00pm, Monday to Friday (except public holidays). **1800 642 428**

Be sensitive to the diversity of patients on ODT.

- Some cultures will have restrictions around the gender of the person who can give them an injection.
- There may be cultural issues around injecting in particular sites.
- Using a professional interpreter is always preferable to using a family member, for clearer, unbiased, and confidential exchange of information.
- Be aware of how ODT is provided in correctional facilities and recognise that some patients transferring from correctional facilities may need different support in the community than they did in correctional facilities.

The best therapeutic relationships are built on respect, cooperation, neutral information sharing, and an honest and open exchange that balances clinical responsibilities with patient treatment goals.

Be aware that LAIB may result in a decrease in attendance for medication taking, and this will vary between patients.

Although LAIB provides a potential for less frequent attendance, the difference in number of visits will vary widely. The difference may depend on how frequently patients attended previously, whether they opt for a weekly or monthly LAIB, and/or what plans are in place for clinical review.

Access LAIB injection training to reduce your patient's pain and discomfort.

The product viscosity of LAIB formulations is greater than that of many other subcutaneous injections. Adverse events involving the injection site are common. For more information, see Chapter 6: Administering LAIB injections.

Table 1. Potential changes for patients transitioning to LAIB

LAIB factor	May result in	Potential benefits	Potential downsides	Think about/discuss with your patient
Less frequent attendance at dosing sites	Reduced travel	• Reduced travel time • Reduced travel expenses • Reduced risks associated with travel (e.g. driving, falls)		
	Change in daily/weekly patterns	• Fewer appointments to keep track of • More time and freedom to participate in work, family, relationships, travel, study	• Destabilisation of routine and daily/weekly structure • Feeling lost with nothing to do	• What are you planning to do with the time a switch to LAIB will give you? • How does this change your options for travel, study, employment and other activities?
	Reduced attendance at dosing site	• Reduced experience of stigma and discrimination through visibility of regular attendance • Decreased contact with people at the dosing site who the patient may wish to avoid	• Disrupted engagement with health and other social services provided at dosing site • Social disconnection from positive relationships within clinic	• How will you and your patient work together to ensure they remain supported and connected to services and people?
	Reduction in missed doses for people struggling to attend regularly	• Enhanced treatment outcomes • May help in avoiding cycle of missed doses, polydrug use, and subsequently deteriorating health and social conditions	• Reduced autonomy in deciding how and when to take ODT medication	
Administered directly by health professionals		• Reduced risk/temptation for diversion and non-medical use (unprescribed injecting or stockpiling) • Provides greater availability to ODT in custodial settings	• Patient may have to alter usual patterns of engaging with their treatment and substance use	

LAIB factor	May result in	Potential benefits	Potential downsides	Think about/discuss with your patient
Long-acting, slow release formulation		• Patients may be less drowsy, more alert • Patients may experience less severe withdrawal on cessation of LAIB than SL BPN	• Patients may have less personal control over how they take their ODT medication	

1.3.1 In the words of a consumer ...

The below words were written by a person in NSW with lived and living experience of LAIB. No words have been changed.

This description is one experience and is not intended to generalise the range of ways that people respond to LAIB.

Three words describe my treatment journey. Flexibility, unrestrained, and spontaneity.

I got a sense of liberty. Only having to go to the clinic once a month.

I now have some flexibility with my days/weeks.

I'm not weighed down with daily visits to the clinic.

Depot Bupe has been my passport to a new life.

Monthly depot has been a game changer for me.

Because I can study or work, I have a new outlook on life.

I feel like the lights have been turned on all of a sudden.

I have a sense of self-determination now.

My life is not rote anymore.

This treatment is workable and gives me leeway to choose what I now have available to me.

The best advice I got before starting Depo Bupe was ‘explore all things you thought of doing.’

It works for me, and it may work for you.

This treatment has given me the courage to attempt new things/lifestyle.

Monthly Bupe is a courageous move.

1.3.2 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 and key medical, psychiatric, and social complications, and examine patient treatment goals and preferences. It may take several appointments to complete the assessment. Details regarding assessing patients for ODT are described in national and local guidelines [2, 3].

Patients are important partners in treatment planning and should be active participants in all stages of the treatment process (i.e. assessment, treatment planning and review), and reflect the patient's preferences, circumstances and case complexity. Assessment and planning often involves coordination across multiple health and welfare providers. A treatment care plan that addresses the patient's substance use, physical and mental health, and social issues should be developed and documented with patients.

Informed consent is critical. Patients should understand the implications of different treatment options, including potential risks and benefits, side effects, medication frequency, and financial and other commitments.

Patients in focus

To support patient understanding, consider these tips from the NSW Health Literacy Framework:[9]

- Use plain language.
- Take into account your patient's culture, mental state, preferences, age and disability, including hearing and vision loss.
- Use interpreters when patients need assistance communicating in English or have a hearing impairment.
- When speaking to patients, confirm you understand them and they understand you by using a tool such as Teach-back, available at teachback.org.
- Ask patients with disability about aids they normally use, e.g. visual aids and communication boards, and use them when communicating.
- Conduct follow-up calls to ensure patients understand their care plan.
- Refer patients to reputable resources (print, audiovisual and websites) for further information.
- Ensure resources are tested and approved by consumers from the target population, approved by their organisation for distribution, available in priority community languages, and in accessible formats.

Scheduling

Conventional ODT with methadone and SL BPN treatment usually involves frequent attendance for (supervised) dosing, which provides the opportunity to schedule regular clinical reviews, medical appointments and psychosocial interventions (e.g. counselling). For example, the National Guidelines for Medication-Assisted Treatment of Opioid Dependence [3] 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 patient and service providers may be developed.

One option may be to consider using the weekly LAIB formulation (Buvidal Weekly) when commencing treatment (e.g. for the first two to four weeks) until individual patient treatment needs are clarified.

[9] https://www.cec.health.nsw.gov.au/improve-quality/teamwork-culture-pcc/person-centred-care/health-literacy

1.3.3 LAIB compared with other ODT preparations

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 the National Guidelines for Medication-Assisted Treatment of Opioid Dependence (S A.4.1) [3] and NSW Guidelines (including the NSW OTP Guidelines).[10]

Patient factors

- prior experience with medications
- adverse events
- drug–drug interactions (DDIs)
- overdose risks
- flexibility of dosing options with BPN
    - SL BPN options: alternate-day dosing and unsupervised dosing
    - LAIB options: weekly or monthly dosing.

Clinician factors

- accreditation of medical practitioner to prescribe one medication over another
- clinician familiarity with different medications.

There is minimal research evidence to guide decisions regarding the choice between the LAIB formulations (Buvidal Weekly, Buvidal Monthly and Sublocade) and SL BPN treatment. Individual patient and clinician factors need to be considered (see Table 2: Differences between SL and LAIB [Buvidal and Sublocade]).

For patients on four-weekly LAIB injections, clinical reviews may be organised in between medication visits for patients initiating ODT, or during periods of clinical instability during which assessment, care planning activities and psychosocial interventions are attended to.

[10] https://www.health.nsw.gov.au/aod/Pages/nsw-clinical-guidelines-opioid.aspx

Table 2. Differences between SL and LAIB (Buvidal and Sublocade)

	Sublingual formulations	Buvidal (weekly and monthly LAIB)	Sublocade (monthly LAIB)
Taking medication 	Requirements are influenced by local jurisdictional guidance and implemented by individual clinicians. It is recommended treatment with SL BPN is supervised at the onset of treatment, with increasing access to takeaway and unsupervised dosing according to a risk–benefit assessment. Alternate-day and three-day dosing are options for some patients, but are often ineffective for patients on high daily doses (e.g. 24 mg or more).	LAIB can reduce the need for regular attendance at a pharmacy or clinic to take medication. This may be particularly relevant for those who are unable to attend regularly (due to travel, work, childcare, health or housing concerns), and particularly for those patients considered unsuitable for large numbers of SL BPN takeaway doses (e.g. due to substance use, social circumstances, poor treatment engagement and/or other health conditions). See the NSW OTP Guidelines for more information.	
If on current low SL BPN dose 	Patients effectively treated with low daily SL BPN doses (<4 mg) may not wish to increase their 'BPN levels' by transitioning to LAIB – particularly monthly formulations.	The lowest Buvidal Weekly dose (8 mg) is broadly equivalent to 2–6 mg SL BPN daily; whilst the lowest Buvidal Monthly dose (64 mg) is broadly equivalent to 8–10 mg SL BPN daily. Patients effectively treated with low daily SL BPN doses (<8 mg) may elect not to increase their BPN levels by transitioning to monthly LAIB doses. Consider use of Buvidal Weekly for these patients.	100 mg Sublocade doses are equivalent to moderate (e.g. ≥8 mg) SL BPN doses, with the 300 mg Sublocade dose equivalent to SL BPN doses >16 mg. Patients effectively treated with low daily SL BPN doses (<8 mg) may be unwilling to increase their BPN levels by transitioning to Sublocade and Buvidal Monthly. Buvidal Weekly may be the preferred LAIB medication.
Previous exposure and experience with BPN 	Patients with no prior BPN exposure should have a period of SL treatment that is sufficient to establish if there are any ongoing concerns with BPN treatment (adverse events, DDIs, etc.) warranting its discontinuation. This can generally be established rapidly with SL BPN (e.g. within seven days).	Patients with prior BPN exposure should have a good understanding of any likely adverse events or DDIs that will be relevant to them, and can commence LAIB either directly (e.g. Buvidal) or after a period of SL BPN treatment (Sublocade, Buvidal).	
		Patients commencing BPN treatment (e.g. from heroin or other opioids) can be initiated directly on to Buvidal Weekly. Patients can be transferred to Buvidal Monthly after treatment initiation with Buvidal Weekly.	Patients should have a period of treatment with BPN (either SL BPN ≥8 mg or Buvidal treatment for at least seven days) prior to commencing Sublocade treatment.

	Sublingual formulations	Buvidal (weekly and monthly LAIB)	Sublocade (monthly LAIB)
Duration between doses 	SL BPN dose interval is usually 24-hours, whilst two- and three-day intervals can be effective for many (but not all) patients.	Buvidal Weekly enables dosing every five to nine days, and possibly up to 14 days for some patients. Buvidal Monthly enables dosing every three to five weeks, and up to six weeks for some patients. Individual variation will occur.	Sublocade enables dosing every 26 to 42 days, and up to eight weeks for some patients. Individual variation will occur.
Side effects	In general, adverse events to BPN are similar for both SL and LAIB, except for local injection-related adverse events, which tend to be transient and mild in most cases.		
	It is easier to adjust the BPN dose and even discontinue ODT when using SL BPN.	If there are concerns regarding BPN-related adverse events (e.g. severe hepatic disease), patients should be initially treated and stabilised on SL BPN, allowing for assessment and management of adverse events before transitioning to LAIB. Moderate or severe injection-related adverse events that do not spontaneously resolve are a reason to ensure good subcutaneous injection technique is occurring. Consider: • using the alternate LAIB formulation, or • discontinuation of LAIB and transition to SL BPN treatment.	
Drug interactions 	In general, BPN DDIs are similar for both SL and LAIB formulations. The ease of dose adjustment with SL BPN treatment suggests it should be preferred if there are concerns regarding potential clinically significant DDIs.	If there are concerns regarding significant DDI, consider a period of treatment with SL BPN enabling easier dose titration (and discontinuation if required). See Appendix A for DDI list.	
Goal of withdrawal from ODT 	Withdrawal usually involves gradual taper of SL doses over weeks to months. Withdrawal is associated with relapse to opioid use, with an increased risk of opioid overdose in the period after ceasing ODT. Overdose prevention strategies (e.g. take home naloxone [THN]) and aftercare are advised.	Withdrawal usually involves cessation from the lowest dose available (e.g. Buvidal Monthly 64 mg, Buvidal Weekly 8 mg, Sublocade 100 mg), and as such can occur in a shorter timeframe than taper of SL BPN. Whilst it appears that cessation of LAIB treatment is usually associated with mild opioid withdrawal symptoms, it remains unclear whether stopping LAIB results in different outcomes (relapse rates, health outcomes including overdose, patient experience) than withdrawal from SL formulations.	

	Sublingual formulations	Buvidal (weekly and monthly LAIB)	Sublocade (monthly LAIB)
Wrap-around support	Frequent attendance may afford greater opportunities to provide wrap-around support to patients and for clinicians to stay connected to patients' changing goals.	Clinicians should maintain regular contact with patients. They should find out what their goals are and develop a plan with patients for how these can be supported when attendance for medication is reduced.	
Pregnancy and breastfeeding 	Australian clinical guidelines support the use of SL BPN as a first line agent alongside methadone for opioid dependence in pregnancy and during breastfeeding. SL BPN should be considered as the first line agent for women with opioid dependence not already in treatment. Switching to BPN from methadone is not recommended in pregnancy. Neonates should be screened and treated for neonatal opioid withdrawal if this emerges. Paediatric follow-up is recommended for children exposed to opioids and other drugs in utero. Although there is a lack of published literature, breastfeeding is generally recommended for women on SL BPN.	There is limited research data on the outcomes of LAIB treatment during pregnancy for pregnant women and their baby. A risk–benefit assessment regarding choice of BPN formulations (weekly or monthly LAIB) should be undertaken with pregnant/breastfeeding women. Continuing treatment with LAIB during pregnancy may be appropriate for women who have already stabilised well on LAIB, or transfer to LAIB may be considered for a pregnant woman who has not stabilised well on SL BPN treatment. Transfer from LAIB to SL BPN treatment may be considered for pregnant women; however, the risk of destabilising the patient who had been progressing well on LAIB, and consequent risks of opioid and other drug use, need to be considered. Although there is a lack of published literature, the benefits of breastfeeding will usually outweigh risks for women on LAIB. For more information, see Chapter 11: Pregnancy, breastfeeding and contraception.	
Unstable medical, psychiatric and social conditions	Patients with unstable clinical presentations often require frequent clinical reviews and interventions.		
	Frequent attendance for SL BPN medication can provide an opportunity to better engage some patients.	Many patients can be effectively treated with Buvidal Monthly; however, consider Buvidal Weekly (or SL BPN) for patients that require more frequent monitoring.	Many patients can be effectively treated with Sublocade; however, consider Buvidal Weekly (or SL BPN) for patients that require more frequent monitoring.
Takeaway/ unsupervised medication taking 	Medication provided as 'takeaways' and/or unsupervised regimens are appropriate for patients assessed as low-moderate risk of safety concerns (e.g. non-medical use of medications, overdose) and enhance patient autonomy (see the NSW OTP Guidelines for more information). Some patients do not meet eligibility requirements for frequent takeaway or unsupervised dosing.	LAIB may be preferred where a patient has multiple risk factors for takeaways or unsupervised dosing that are difficult to mitigate. LAIB should not be given to patients for handling or self-administration.	

2. Opioid dependence treatment in NSW

2.1 The NSW Opioid Treatment Program (OTP)

The OTP seeks to reduce the social, economic and health harms associated with opioid use. It delivers pharmacotherapy and associated services to patients with opioid dependence in NSW.

All accredited and non-accredited OTP prescribers can prescribe and administer LAIB medicines, Buvidal and Sublocade.

See the NSW Health OTP website[11] for details about:

- accreditation information
- requirements for notifications (e.g. changes to dosing point, locum arrangements).

Non-accredited OTP prescribers

Medical practitioners who are not accredited OTP prescribers may manage up to 30 patients on ODT, including:

- up to 20 patients treated with SL BPN or BPN-naloxone, or LAIB
- up to 10 patients treated with methadone who have been inducted and referred by an accredited OTP prescriber.

Accredited OTP prescribers

Any medical practitioner or nurse practitioner who is an accredited OTP prescriber may prescribe LAIB as part of their patient limit of 200. Practitioners working in public OTP clinics may prescribe for up to 300 patients. Prior approval of the Secretary, NSW Health (or delegate) is required to exceed this limit.

[11] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/otp-medical-practitioners.aspx

2.2 Legislation and regulation of LAIB

Like other ODT medicines, LAIB formulations are Schedule 8 Drugs of Addiction. Usual provisions apply as outlined in the relevant legislation.[12] Further guidance is available on the NSW Health website.[13]

At the time of publication, the *Poisons and Therapeutic Goods Act 1966* and *Poisons and Therapeutic Goods Regulation 2008* remain in force.

Future changes

The *Medicines, Poisons and Therapeutic Goods Act 2022* (MPTG Act) has passed Parliament and, on commencement, will repeal the *Poisons and Therapeutic Goods Act 1966*.

As part of this legislative change, it is proposed that OTP Standards are introduced for prescribing, supplying and administering methadone and BPN for the purposes of the OTP.

The new legislation, regulatory framework and OTP Standards are expected to come into force in 2025.

2.2.1 ODT medication available through the PBS

Since 1 July 2023, all ODT has been available in Australia thorough the PBS as part of the Section 100 Highly Specialised Drugs (HSD) Program (Community Access) arrangements.

Under the Section 100 HSD Program, PBS-eligible patients will pay the PBS co-payment to access their treatment (for up to 28 days' supply per pharmaceutical benefit prescribed) and the amount paid will contribute towards their PBS Safety Net threshold.

Additional private dispensing or dosing fees cannot be charged.

2.2.2 Approval to prescribe and supply LAIB

As per other ODT medicines, all prescribers of LAIB must obtain approval from NSW Health, which must be granted prior to a patient commencing treatment in an outpatient setting. Refer to the OTP webpage [14] on the NSW Health website for information about how to obtain approval.

Refer to this webpage[15] for up-to-date information about the requirements for approval to use ODT in an inpatient setting.

Approval to transfer between medication types

Approvals to prescribe BPN are not specific to dosage form. The practitioner may be authorised to use BPN in SL and/or injectable form, together or separately. A new approval is not required to switch a patient from one form of BPN to another, or when using both forms concurrently. However, a switch to methadone from BPN, or vice-versa, will require a new approval.

For information regarding approvals for microdosing and bridging transfer protocols, see Appendix C.

[12] www.health.nsw.gov.au/pharmaceutical/Documents/guide-medprac-nurse-dentist.pdf

[13] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/guides-legislation-medical-practitioners.aspx

[14] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/otp-medical-practitioners.aspx

[15] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/otp-in-hospital-inpatients.aspx

2.2.3 Prescriptions

Prescribers must ensure that all prescriptions for LAIB are compliant with local jurisdictional regulations for Schedule 8 opioid medications and federal legislative requirements.

Prescriptions for LAIB must be signed by the prescriber, and include the following details:

Item	Detail required	Example(s)
Date	The date the prescription is issued.	02/04/2024
Patient details	Name, date of birth and address.	John Smith 11/05/1974 1 Smith Street, Smithville NSW
Prescribing doctor or nurse practitioner's details	Name, designation, practice address and contact details.	Dr Judy Hamilton Eastside Clinic, 4 McDonald Avenue, Bluesville NSW 2222 Phone: 02 9999 9999
The drug to be supplied	Name and strength. Confirm any dose that could be regarded as being dangerous or unusual by underlining the part of the prescription that specifies the intended dose and by initialling the prescription in the margin. Quantity. Expressed in both words and figures.	Buprenorphine 128 mg injection (Buvidal Monthly) 1 (one)
Dosage directions	Adequate directions for use, and route of administration.	subcutaneous/SC, every 3 to 5 weeks or subcutaneous/SC, every 21 to 35 days
Number of repeats, and the repeat intervals at which the drug may be supplied	The **repeat** is the maximum number of times the prescription can be dispensed (in addition to the original). The interval is the **minimum number of days between dispensing**. The **supply interval** does not need to match the **clinical dosing** interval. For example, if the medicine is to be administered once a month, it may be necessary for the supply interval to be 21 days, as the prescription may need to be dispensed a few days earlier in preparation.	2 (every 21 days)

2.2.4 SafeScript NSW

SafeScript NSW[16] is an online prescription monitoring and approval management system. It allows:

- prescribers and pharmacists to access real-time information about their patient's prescription history
- prescribers to submit and manage applications for approval to prescribe or supply Schedule 8 medicines under the OTP
- health practitioners to add and update dosing points, allowing those involved in patient care to have clarity on where the patient is being dosed.

Further SafeScript NSW resources:

- Refer to the Approval Management[17] section of the SafeScript NSW website for detailed information on functionality, as well as support material, FAQs, etc.
- SafeScript NSW Online Help[18] provides technical information and screenshots of key functionality.
- How to set up your account[19] is a quick reference guide for prescribers.

If you are unable to apply for authority management through SafeScript NSW, see the NSW Health website[20] for more information about application for approval to prescribe.

2.2.5 Drug registers

The usual provisions for Schedule 8 Drug Registers apply. This requires that a record be made in a drug register of all LAIB formulations obtained, supplied, or administered.

2.2.6 Patient documentation

An authorised practitioner who prescribes a drug of addiction must make a record of the particulars listed above in section 2.2.3 Prescriptions.

The record must be kept at the surgery, hospital or office of the person prescribing the substance.

The medical practitioner or nurse practitioner must also record the above particulars of administration in the drug register.

[16] www.health.nsw.gov.au/safescript

[17] www.health.nsw.gov.au/pharmaceutical/safescript/practitioners/Pages/approval-management.aspx

[18] help.safescript.health.nsw.gov.au/nsw-hp.htm

[19] www.health.nsw.gov.au/pharmaceutical/safescript/practitioners/Pages/how-to-set-up-your-account.aspx

[20] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/otp-medical-practitioners.aspx

3. Clinical pharmacology

BPN 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 BPN are dose dependent within a limited range, above which increasing dosages do not produce corresponding increases in effect. Thus, for certain pharmacologic effects (e.g. respiratory depression and sedation), BPN may exhibit an enhanced safety profile compared with mu-opioid receptor full agonists. The clinical relevance of BPN activity at kappa-opioid receptors remains unclear. Extended-release BPN formulations (e.g. 'low-dose' 7-day transdermal BPN patches) have long been available for the treatment of pain, and now the LAIB formulations Buvidal Weekly [10], Buvidal Monthly [11] and Sublocade [12] are a new generation of extended-release 'medium-high dose' BPN formulations for the treatment of opioid dependence [13].

3.1 Formulations

3.1.1 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 ½-inch, 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 four dose strengths in prefilled syringes with a ½-inch, 23-gauge needle: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL or 160 mg/0.45 mL BPN as the active ingredient.

Buvidal depots contain the active substance BPN in delivery system compositions based on the proprietary FluidCrystal injection depot technology – a lipid-based liquid. When injected into the SC tissue the FluidCrystal formulation absorbs interstitial aqueous body fluid and transforms from liquid to highly viscous liquid crystal (or gel-like) phases in situ, which effectively encapsulate the active substance. This results in a slow and consistent release of BPN, which can be controlled for a week or a month depending on the composition. Excipients are described in Appendix B.

3.1.2 Sublocade formulations

Sublocade is an extended-release formulation of BPN, administered monthly by SC injection, and provides sustained plasma levels of BPN over the monthly dosing interval. Sublocade utilises a proprietary BPN gel depot delivery system (Indivior's delivery system). Sublocade is injected as a liquid, and subsequent precipitation of the polymer creates a depot containing the BPN. After initial formation of the depot, BPN is released via diffusion from, and the biodegradation of, the depot.

Sublocade is available in two dose strengths: 100 mg/0.5 mL and 300 mg/1.5 mL provided in a prefilled syringe with a ⅝-inch, 19-gauge needle.

3.2 Overview of pharmacokinetic properties

The key pharmacokinetic properties of Buvidal and Sublocade are detailed in the product information documents (Appendix B) and summarised in this section for comparison between the two formulations.

Repeated use of LAIB formulations results in accumulation over time, and steady state equilibrium is 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 LAIB and SL BPN formulations are shown in Figure 1: Pharmacokinetic parameters at BPN steady state equilibrium, allowing a framework for comparing dose effects across different formulations.

Dose-proportional increases are seen within each category (SL, weekly and monthly) of BPN formulations. However, there is considerable variation in BPN plasma levels between individuals, and these should only be interpreted as a guide.

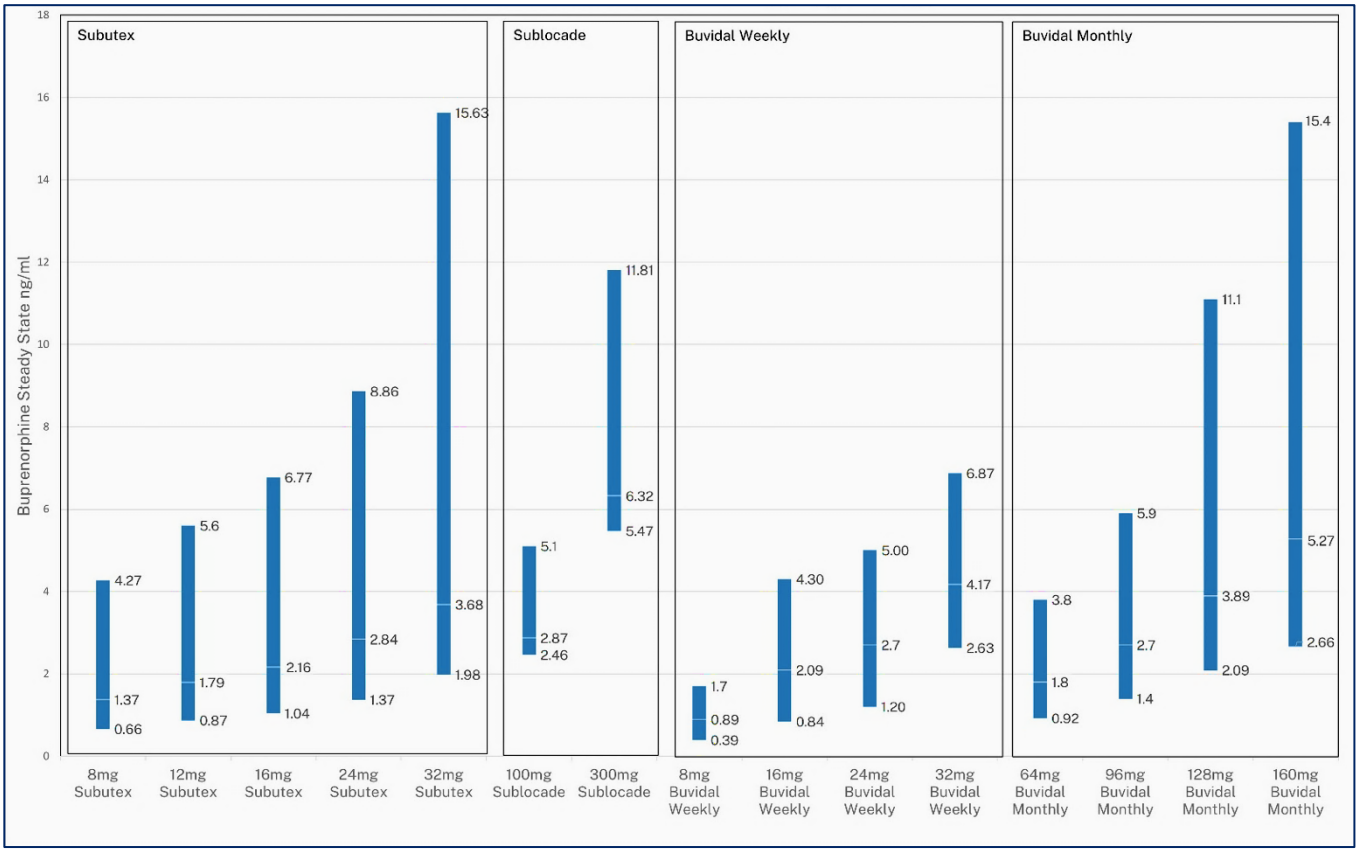
Brain imaging studies suggest that the suppression of signs and symptoms of withdrawal may require ≥ 50% μ-opioid receptor occupancy (μORO), which is often associated with BPN plasma concentrations ≥ 1 ng/mL; whereas opioid blockade (defined as the inhibition of the positive subjective effects [i.e. drug liking] of exogenous opioids) appears to require higher proportion in many individuals (e.g. ≥ 70–80%) μORO [14], often associated with higher BPN plasma concentrations (e.g. ≥ 2–3 ng/mL [11, 12]. These plasma levels are generally achieved by all LAIB formulations.

Whilst laboratory receptor-binding studies are of interest in our understanding of this treatment approach, they do not translate into clinical practice readily, and there is no clinical role for monitoring BPN plasma levels as part of routine patient care. At this time, there is an inability to routinely or meaningfully measure BPN (or its active metabolite nor-BPN) plasma levels or to assess opioid-receptor occupancy in clinical practice: few laboratories have the capacity to accurately quantify BPN and nor-BPN levels, tests are not reimbursed by Medicare and findings are very difficult to interpret – clinicians should focus upon individual patient responses to treatment, with reviews of patient experience of withdrawal, cravings, continued substance use and adverse events. 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 BPN dose is not the only factor to be considered.

Plasma BPN levels only partially account for the clinical (pharmacodynamic) effects experienced by patients – such as prevention of opioid withdrawal or blockade effects. A range of other factors impact upon the clinical effects of BPN and must be considered when titrating BPN doses to achieve desired clinical outcomes – including patient expectancy, concomitant medical (e.g. chronic pain, hepatic disease) and mental health conditions, use of other opioids and substances, drug–drug interactions, adverse events and genetic variation. Whilst expected plasma concentrations routinely achieved with formulations can serve as a guide to the selection of BPN doses and formulation,

regular clinical patient monitoring is required. As previously highlighted, therapeutic monitoring of BPN plasma levels in clinical practice is not currently recommended.

Figure 1. Pharmacokinetic parameters at BPN steady state equilibrium. Subutex, Sublocade and Buvidal C_{min} C_{avg} and C_{max}



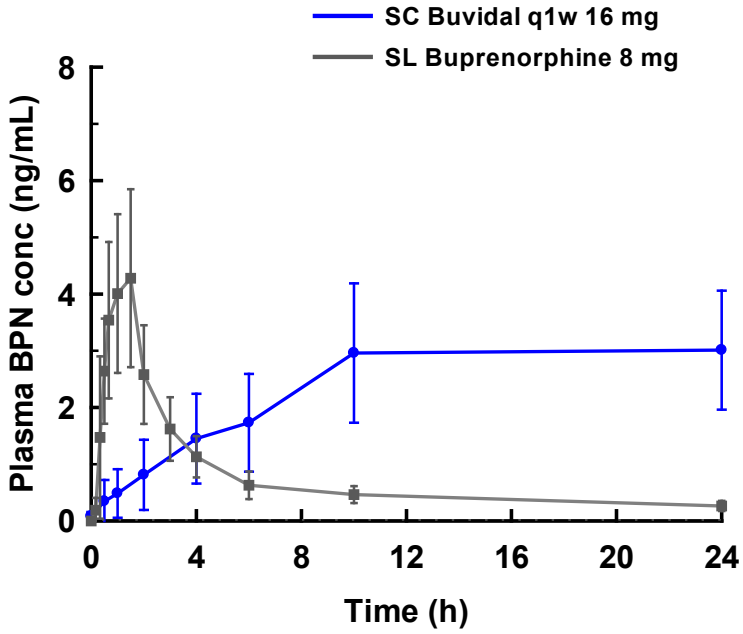
Note: In Figure 1, Buvidal is represented as a mix of modelled data from Camurus data on file [15] (8 mg and 24 mg Weekly doses and 64 mg and 96 mg Monthly doses) and measured data presented in the European Public Assessment Report for Buvidal [16] (16 mg and 32 mg Weekly doses and 128 mg and 160 mg Monthly doses). All figures presented are geometric means.

3.2.1 Absorption and onset of effects

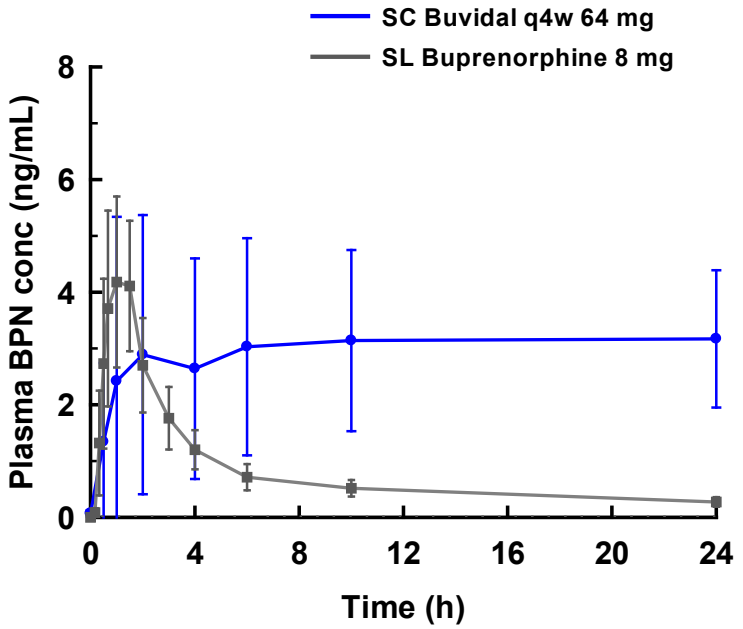
After SC injection, onset of BPN effects commence within one to two hours of dosing, with BPN peak concentrations observed approximately six to 10 hours after the Buvidal Monthly injection, and approximately 24 hours after the Buvidal Weekly and Sublocade injections. After the initial BPN peak, the plasma BPN concentrations decrease slowly until the next dose is administered.

Figure 2. Plasma BPN concentration following a single dose of 8 mg SL BPN and subsequent a) Buvidal 16 mg dose (weekly) and b) Buvidal 64 mg dose (four-weekly)

a



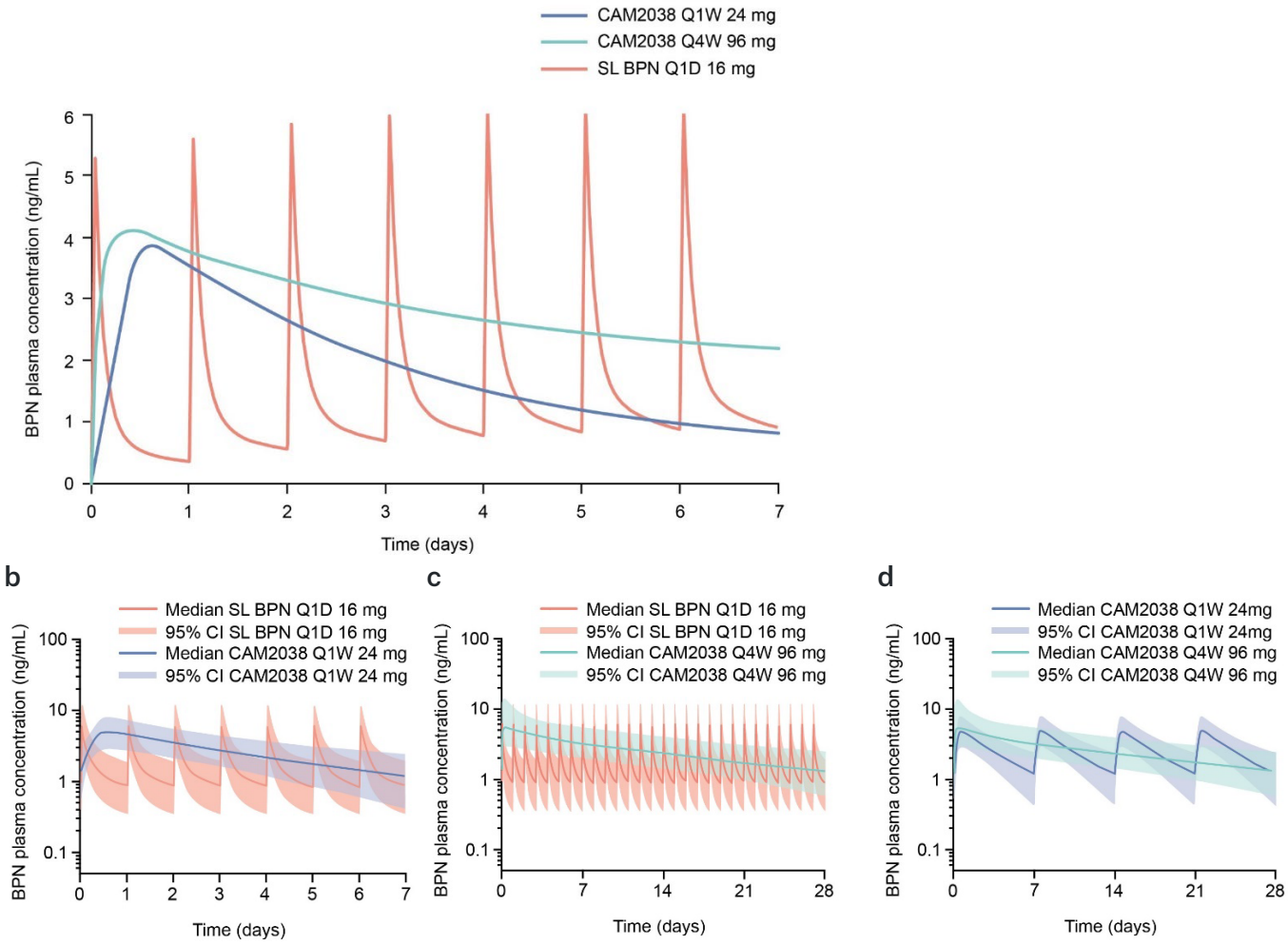
b



q1w = once weekly, q4w = once four-weekly.

Note: Figure 2 is taken from Phase 1 trial data, obtained from Camurus data on file (a, 2014 and b, 2017). Study data also published as Albayaty et al., 2017 (graphs not included) [17].

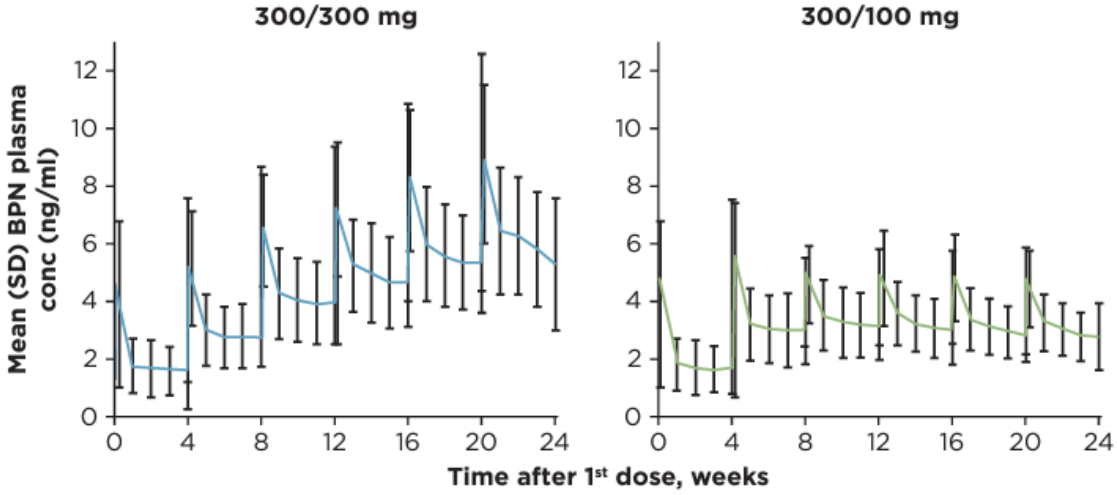
Figure 3. Plasma concentrations of Buvidal Weekly and Buvidal Monthly versus daily SL BPN



CAM2038 = Buvidal, Q1W = weekly, Q4W = monthly, Q1D = daily.

Note: Figure 3 shows modelled data from Phase 1 and 2 trials [18].

Figure 4. Plasma concentrations of Sublocade for 300/300 mg and 300/100 mg regimens



Note: Figure 4 is taken from Phase 3 trial data, showing PK profile during four-weekly Sublocade injections. Reprinted with permission [9].

3.2.2 Distribution

BPN is lipophilic and has a large volume of distribution. BPN is highly protein bound (96%), primarily to alpha and beta globulin.

3.2.3 Metabolism

The metabolism of BPN is largely the same irrespective of LAIB formulation. Variation in plasma terminal half-life and duration of effect is related to differences in the rate of release of BPN from the depot from the three different formulations. BPN is predominantly metabolised (N-dealkylation) by cytochrome P450 (CYP3A4) to the active metabolite nor-BPN, and both parent molecule and metabolite then undergo glucuronidation. Subcutaneous administration of LAIB results in significantly lower plasma concentrations of nor-BPN metabolite compared to SL BPN, due to avoidance of first-pass metabolism invariably seen with some oral swallowing of SL doses.

3.2.4 Elimination and duration of effects

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

- Buvidal Weekly: three to five days
- Buvidal Monthly: 19 to 25 days
- Sublocade: 43 to 60 days.

Steady state

With repeated dosing, BPN plasma levels accumulate until steady state equilibrium is achieved typically by four to six 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, four months for Buvidal Monthly).

For Sublocade, steady state equilibrium is generally achieved after four to six doses of the 300/300 regimen. In contrast, steady state equilibrium is achieved after the third dose of a 300/100 regimen (as the first two 300 mg monthly doses are loading doses, and plasma levels reach steady state following the first 100 mg dose; see Figure 4 above).

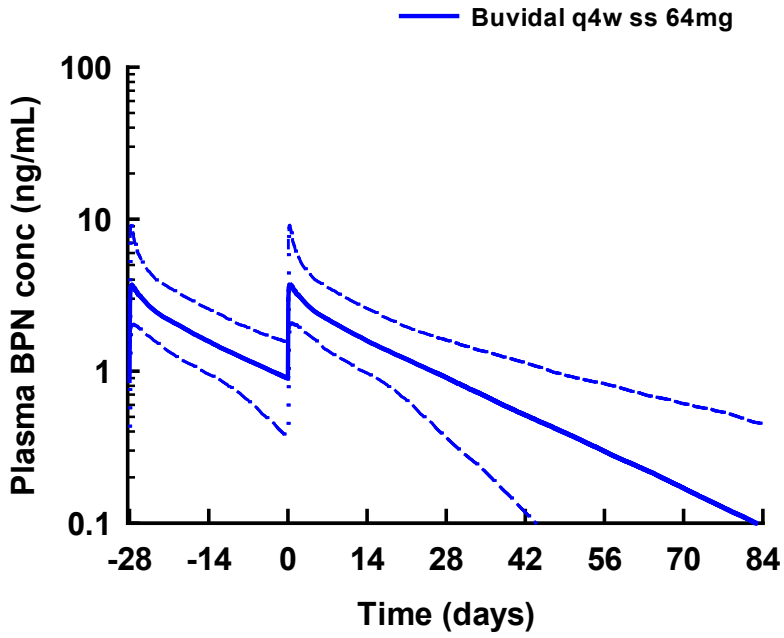
Plasma levels following discontinuation

The clinical effects of discontinuing LAIB dosing will depend upon the formulation administered (weekly or monthly), the dose of depot administered (longer duration with higher doses), and the duration of treatment (whether steady state has been achieved following multiple doses). Model simulations and clinical experience indicate that steady-state BPN plasma concentrations decrease slowly over time following the last injection, with persistent BPN plasma levels for extended periods – potentially up to three to five half-lives for each formulation (hence two to four weeks after last Buvidal Weekly dose, eight to 16 weeks after last Buvidal Monthly dose, and up to 16 to 30 weeks for Sublocade dose).

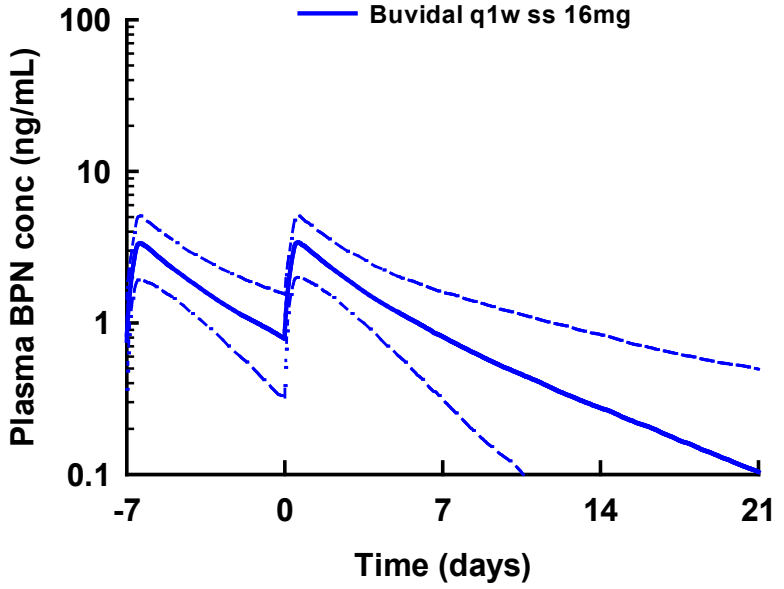
BPN may be detected for extended periods of time in urine drug screens or plasma assays of patients treated with LAIB after the cessation of dosing. The long half-lives of Buvidal Monthly and Sublocade can result in detectable levels of BPN for many months after last dose, beyond the period of therapeutic action. Specialist toxicology advice is recommended in interpreting laboratory urine drug screens or plasma assays in people treated with LAIB.

Figure 5. Predicted decrease in BPN plasma concentrations for Buvidal dosing regimens following discontinuation from steady state, a) Monthly 64 mg, and b) Weekly 16 mg

a



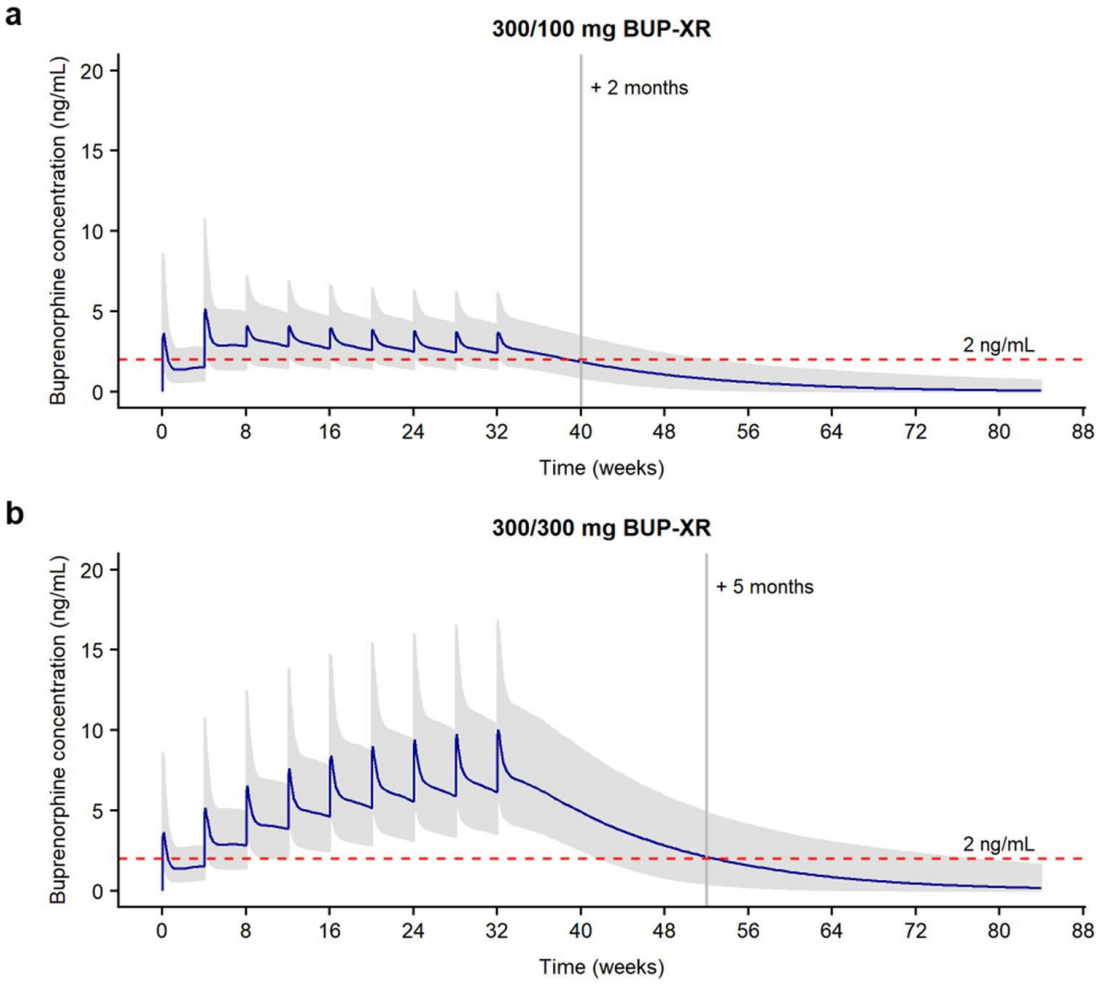
b



q1w = once weekly, q4w = once four-weekly, ss = steady state.

Note: Camurus Data on File (2024)

Figure 6. Predicted decrease in BPN plasma concentrations for Sublocade dosing regimens following last dose



Note: 'Blue solid lines: median of the simulated data; gray shaded areas: 90% prediction intervals of simulated data. The horizontal red dashed line indicates the 2-ng/mL minimum concentration required for opioid blockade' [19]. Reprinted with permission.

The prolonged duration of effects of depot formulations may impact upon the (delayed) emergence of withdrawal symptoms, experience of adverse events, drug–drug interactions and transitioning onto other opioid medications (e.g. SL BPN, methadone). It may also result in delayed 'reduction' of tolerance to opioids and provide temporary protection against overdose following resumption of heroin or other opioid use (whilst plasma levels of BPN remain circulating for several half-lives after cessation of LAIB treatment) [14].

3.2.5 Withdrawal, cravings and opioid blockade

Clinical trials indicate that both Buvidal [8] and Sublocade [9] are effective in reducing opioid withdrawal symptoms and cravings for opioid use. Withdrawal symptoms from stopping Buvidal or Sublocade are described in section 7.1 Withdrawing from LAIB (with goal of opioid abstinence).

'Opioid blockade' is defined as the inhibition of the positive physiological and subjective effects (i.e. drug liking) of exogenous opioids. It is achieved by BPN due to its greater affinity for mu-opioid receptors than conventional opioids such as morphine, heroin, methadone and oxycodone. The blockade of subjective opioid effects has been demonstrated with laboratory hydromorphone challenge studies with Buvidal Weekly and Sublocade formulations.

Although studies demonstrate the blockade of opioid agonists used in addition to LAIB, some patients continue to use opioids in addition to LAIB. Treatment with lower LAIB doses (e.g. 64 or 96 mg Buvidal, 100 mg Sublocade) will produce less effective blockade than higher LAIB doses. Some patients may report an attenuated (milder or shorter duration) rather than a complete blockade of effects from additional opioid use, and higher LAIB doses are likely to produce greater blockade effects. Some patients continue to use opioids in addition to LAIB despite experiencing minimal pharmacological opioid effects; continued opioid or other substance use may be linked to behavioural and/or expectancy issues (and warrant a psychosocial rather than pharmacological response).

4. Side effects and safety issues

4.1 Adverse effects

Adverse effects of LAIB are similar to the known safety profile of BPN administered sublingually [2, 3], with the exception of adverse events related to injection of the drug [13]. Refer to Appendix B for detailed information.

Table 3. Common adverse events to LAIB formulations

	Range %
Injection site–related adverse events	
Pruritus	6.1–9.5%
Pain	4.9–8.9%
Swelling	1.0–4.2%
Erythema	3.0–5.6%
Induration	1.0–1.9%
Bruising	0.5–1.0%
Cellulitis	0.5–1.0%
Other adverse events	
Headache	7.5–8.5%
Constipation	7.5–8.0%
Nausea	7.0–8.9%
Vomiting	4.2–9.4%
Diarrhoea	2.5–2.8%

Note: The ranges in this table represent a combination of the adverse event rates reported in each product information booklet [10–12]. Studies were conducted separately and did not compare formulations against each other.

4.1.1 Contraindications

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

Sublocade should not be administered to patients who have been shown to be hypersensitive to BPN (see below) or any component of Indivior's 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. Hypersensitivity to BPN is very rare.

For further information on contraindications, please refer to the relevant product information, Appendix B.

For additional specialist support and advice for health professionals about LAIB, call the

Drug and Alcohol Specialist Advisory Service (DASAS)

1800 023 687

4.2 Special warnings

4.2.1 Risk of serious harm or death with intravenous administration

Care must be taken to avoid inadvertent or intentional injection of LAIB 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 LAIB forms a depot 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.

4.2.2 Risk of respiratory and central nervous system (CNS) depression

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

4.2.3 Precipitation of opioid withdrawal in patients dependent on full agonist opioids

BPN may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists such as heroin, morphine, or methadone, if the effects of the first dose of LAIB is initiated before the effects of the full opioid agonist have subsided [2,3].

If initiating LAIB (Buvidal only) directly from opioids other than SL BPN (see section 5.2.1 Initiating Buvidal treatment) – there is a potential risk of precipitated withdrawal following the first dose of LAIB if the patient is still experiencing significant opioid agonist effects at the time of first dose, and/or the patient has not disclosed recent use of long-acting opioids such as methadone. Whilst the slow onset of effects of LAIB (Tmax of 24 hours for Buvidal Weekly) suggests that precipitated withdrawal is unlikely to occur when initiating LAIB treatment from heroin or other short-acting opioids, caution should be always exercised, with the first Buvidal dose to be delayed until the patient is not experiencing significant effects from their last use of a short-acting opioid (see section 5.2.1 Initiating Buvidal treatment). It is no longer required to defer LAIB induction until the patient is experiencing significant opiate withdrawal, as recommended for SL BPN, unless the patient has recently consumed methadone. (See section 5.8 Transferring from methadone to LAIB.)

4.2.4 Concomitant use of benzodiazepines or other CNS depressants

LAIB provides higher average blood levels over a weekly or monthly period compared to the daily changes in BPN blood levels with SL BPN. For more information, see section 3.2 Overview of pharmacokinetic properties. Concomitant use of BPN with CNS sedatives (e.g. alcohol, benzodiazepines, tricyclic antidepressants [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 LAIB compared with SL BPN treatments.

For guidance on clinical management, refer to section 8.3.1 Managing risks from concomitant use of benzodiazepines or other CNS depressants.

For additional specialist support and advice for health professionals about LAIB, call the

Drug and Alcohol Specialist Advisory Service (DASAS)

1800 023 687

4.2.5 Hepatitis, hepatic events and liver disease

Moderate or severe hepatic impairment (Child-Pugh B or C) slows down hepatic metabolism of BPN, resulting in higher plasma levels (estimated at 1.6 greater in Child-Pugh B, 2.8 times greater in Child-Pugh C) [21] 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 LAIB has not been studied. Due to the long-acting nature of the formulation, adjustments to LAIB dosages are not rapidly reflected in plasma BPN levels. Because BPN levels cannot be rapidly decreased or adjusted, LAIB should be used with caution in patients with pre-existing severe hepatic impairment (e.g. Child-Pugh B or C).

For guidance on clinical management, refer to section 8.5 Liver disease.

4.2.6 Use in patients at risk of arrhythmia

BPN has been observed to be associated with a prolonged QTc interval in some patients. Whilst in general BPN should be avoided in patients with a history of long QTc 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 QTc interval, existing evidence suggests that QTc prolongation and risk of arrhythmias appears to be greater with methadone, and commonly linked with other substance use, including alcohol, cocaine and amphetamines. A risk–benefit decision should be made regarding opioid treatment for patients at risk of QTc prolongation.

Key differences with LAIB are that serum levels of BPN may be consistently higher than with SL BPN (see section 3.2 Overview of pharmacokinetic properties). For patients at significant risk, more intensive work-up prior to, and/or monitoring whilst on, LAIB treatment may be required. For assessment and management, see section 2.4.8 OAT Safety Issues – QT prolongation in the NSW OTP Guidelines.

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

4.2.7 Other medical conditions

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

- orthostatic hypotension
- elevation of cerebrospinal fluid pressure
- cholestasis
- acute abdominal conditions
- adrenal insufficiency
- poor respiratory function.

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

4.2.8 Driving and operating machinery

BPN has moderate influence on the ability to drive and use machines when administered to patients with opioid dependence. BPN may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and major dose adjustments, and 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 machinery until the prescriber and patient are satisfied that LAIB does not adversely affect their ability to engage in such activities. This is particularly relevant in the first one to four days after the initial LAIB dose, when peak BPN plasma levels are achieved. In general, patients become tolerant to the effects of opioid medication with repeated dosing, and higher LAIB doses may not be associated with

increased risk of impaired driving. Other substance use, and medical and environmental conditions are often key factors in assessing an individual's ability to drive or operate machinery safely.

Jurisdictional regulations on fitness to drive should also be considered. A procedural outline, Managing Driving Safety Awareness for At Risk Clients,[21] is available on the NSW Health website.

For additional specialist support and advice for health professionals about LAIB, call the

Drug and Alcohol Specialist Advisory Service (DASAS)

1800 023 687

4.2.9 Drug–drug interactions (DDIs)

A number of potentially clinically relevant DDIs exist with BPN [2, 3]. Product information (for both Buvidal and Sublocade) indicates interactions:

- with other opioids (precipitated withdrawal, blockade effects)
- that increase the risk of overdose – as occurs with alcohol, other opioid drugs, benzodiazepines, TCAs, pregabalin and gabapentin, sedating antipsychotics, and antihistamines.

Interactions with medications that alter hepatic metabolism. BPN is primarily metabolised in the liver by CYP3A4 enzyme systems, which can be affected by the use of other medications. CYP3A4 inducers will increase the metabolism of BPN (lowering plasma levels), whilst CYP3A4 inhibitors will reduce the metabolism of BPN (increasing BPN plasma levels). There are numerous medications that impact upon CYP enzyme systems (see Appendix B) and considerable genetic variation between individuals, making the clinical effect of such DDIs difficult to predict; patient monitoring is recommended.

Interactions with medications that can precipitate a serotonergic syndrome – most notably monoamine oxidase inhibitors (MAOIs). BPN has been associated with serotonergic syndrome in rare cases, and may be more likely to occur in combination with other medications that increase this risk

Many of these DDIs are difficult to predict, and generally require clinical monitoring and dose adjustment. However, the prolonged duration of effects of the LAIB 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 DDIs, with recommendations regarding management, are described in Appendix A.

[21] www.health.nsw.gov.au/aod/professionals/Pages/driver-safety-example-template.aspx

5. Dosing regimens with LAIB

5.1 Commencing LAIB treatment

Many patients commencing depot treatment in Australia will already be in long-term treatment with SL BPN, enabling a simple transition to LAIB.

For patients who are dependent on heroin or short-acting pharmaceutical opioids (e.g. morphine, oxycodone), LAIB treatment can be commenced directly (with Buvidal Weekly), or after a short period of SL BPN treatment (Buvidal Weekly, Buvidal Monthly or Sublocade).

Transfer from methadone to LAIB has the potential for complications (e.g. precipitated withdrawal, destabilisation), and a range of transfer approaches are available.

5.2 Initiating directly from heroin or other prescription opioids (excluding methadone)

5.2.1 Initiating Buvidal treatment

Buvidal Weekly can be initiated directly from short-acting opioids (e.g. heroin, morphine, oxycodone, fentanyl) without the need for a run-in period of SL BPN treatment. This may be particularly important when:

- the patient has previously experienced BPN treatment and there is no hypersensitivity or other significant adverse events to BPN
- the patient has a preference for initiating depot treatment directly without SL dosing
- the prescriber is confident that the patient has not been using (diverted) methadone in recent days before commencing Buvidal treatment. If in doubt, a point-of-care urine drug test can determine recent methadone use, and this will impact upon treatment decisions (see section 5.8 Transferring from methadone to LAIB).

Whereas initiation of SL BPN treatment recommended delaying the first dose of BPN until the patient was exhibiting features of opiate withdrawal (to minimise the risk of precipitated withdrawal), is not as important a consideration when initiating Buvidal treatment. The delayed onset of action (taking 12–24 hours to reach peak plasma levels) minimises the risk of precipitated withdrawal occurring when initiating a patient using short-acting opioids.

The first dose of Buvidal may need to be delayed if the patient is presenting with features consistent with intoxication to opioids, alcohol or other drugs. A clinical assessment by a suitably skilled clinician is required. Seek specialist advice if in doubt. See section 8.3.2 Intoxicated presentations.

A period of treatment with SL BPN is recommended where there are safety concerns regarding using BPN arising from severe hepatic disease (e.g. Child-Pugh B or C) or DDIs (see Appendix A). Doses of SL BPN are easier to titrate according to clinical response, and LAIB can be considered once the safety of BPN treatment and the logistics of engaging in daily SL BPN dosing for a particular patient are established (considering travel, work or other requirements, local pharmacy SL BPN options, etc.).

When commencing Buvidal Weekly from heroin or other short-acting opioids, a starting dose of 16 or 24 mg Buvidal Weekly is recommended, with the option of additional Buvidal Weekly 8 mg supplementary or 'top-up' doses at least 24 hours apart within the first week as required, to a maximum of 32 mg during the first week. Buvidal is licensed to commence with 16 mg Weekly doses, although clinical experience suggests that patients with higher levels of opioid use may require initiation doses of 24 mg Buvidal Weekly. Patients commencing Buvidal treatment should be instructed that the first dose may 'wear off' before the proposed seven days (which may be experienced as opioid withdrawal symptoms and/or cravings), and that the patient may have the option of attending earlier to receive their second dose (e.g. at day five or six), or may be able to access supplementary Buvidal Weekly 8 mg doses.

The patient should be reviewed by the prescriber or experienced clinician prior to the second week of dosing, assessing the effects (and side effects) of the first dose, patient experience of withdrawal, cravings, and other substance use, with the options of:

- continuing Buvidal Weekly or transferring to Buvidal Monthly (as described in Table 4)
- necessary dose adjustments or titration. Clinical titration of Buvidal doses may be required if the patient presents with significant opioid withdrawal or opioid toxicity (e.g. sedation, nausea, vomiting, or side effects such as agitation, headaches), persistent cravings, or unprescribed opioid use. It should be emphasised that subsequent Buvidal doses after the initial dose become more effective with accumulation of BPN plasma levels until steady state is achieved (usually after three to four doses). Approaches to subsequent titration of Buvidal doses is described in section 5.3.3 Buvidal flexible dosing schedules and missed doses.

5.2.2 Initiating Sublocade treatment

Initiating Sublocade treatment generally requires a seven-day period of treatment with another high-dose BPN medication (e.g. SL BPN ≥ 8 mg daily, or Buvidal treatment) prior to commencing Sublocade.

However, emerging evidence (from case series reports) and clinical experience suggests that Sublocade can be safely initiated after three doses of SL BPN without the need for a full seven-day period of SL BPN treatment. This 'off-label' practice may be appropriate in circumstances where seven days of SL BPN treatment is not feasible (e.g. travel restrictions) and where Buvidal Weekly (licensed for this purpose) is not available. Consultation with an addiction medicine specialist or addiction psychiatrist is recommended.

For additional specialist support and advice for health professionals about LAIB, call the

Drug and Alcohol Specialist Advisory Service (DASAS)

1800 023 687

5.3 Transitioning from SL BPN treatment to Buvidal

5.3.1 Initial Buvidal dose

Patients 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 4: Dose conversion: SL BPN to Buvidal Weekly and Buvidal Monthly.

Factors that may lead to the clinician and patient choosing weekly over monthly treatment may include:

- desire for more frequent (weekly) clinical review due to safety concerns (e.g. arising from concomitant high-risk substance use; unstable medical, psychiatric, or social conditions; potential DDIs)
- patient concerns about LAIB not 'holding' or being effective for an extended period (four weeks).

Available evidence [4, 13] demonstrates that most patients transferring from SL BPN can be safely and effectively treated by initiating Buvidal Monthly injections without the need for a period of weekly dosing.

Table 4. Dose conversion: SL BPN to Buvidal Weekly and Buvidal Monthly

Daily SL BPN dose	Buvidal Weekly depot dose	Buvidal Monthly depot dose
2–6 mg	8 mg	No Monthly equivalent
8–10 mg	16 mg	64 mg
12–16 mg	24 mg	96 mg
18–24 mg	32 mg	128 mg
26–32 mg	No Weekly equivalent	160 mg

The patient should be reviewed by the prescriber (or experienced clinician) prior to the second week of dosing to assess the effects (and side effects) of the first dose, patient experience of withdrawal, cravings, and other substance use, with the options of:

- continuing Buvidal Weekly or transferring to Buvidal Monthly for those initiated on Buvidal Weekly (as described in Table 4)
- necessary dose adjustments or titration, based on the total Buvidal doses administered during the first week or month, patient feedback, and clinical assessment. Increase in Buvidal doses may be required if patients present with significant opioid withdrawal, persistent cravings, or unprescribed opioid use. Dose reductions may be required if patients present with features of

opioid toxicity (e.g. dose-related side effects such as sedation, nausea, vomiting, agitation, headaches). It should be emphasised BPN plasma levels continue to increase with each Buvidal dose until steady state is achieved (usually after three to four doses).

Whilst individual clinical titration of doses may be required on subsequent doses, most patients can usually continue their initial dose without the need for subsequent dose changes. In Australian research [4, 13], approximately 10–20% of patients adjusted their Buvidal dose (up or down) in the subsequent few doses following the initial Buvidal dose.

See section 5.5 Key titration principles – adjusting dose and frequency of doses (CS) for more information.

5.3.2 Supplemental or 'top-up' BPN doses for patients on Buvidal

'Top-up' or supplemental doses of Buvidal may be given if the patient experiences clinical features of opioid withdrawal, cravings, or persistent unprescribed opioid use (see section 5.6 Supplemental BPN dosing for more information).

5.3.3 Buvidal flexible dosing schedules and missed doses

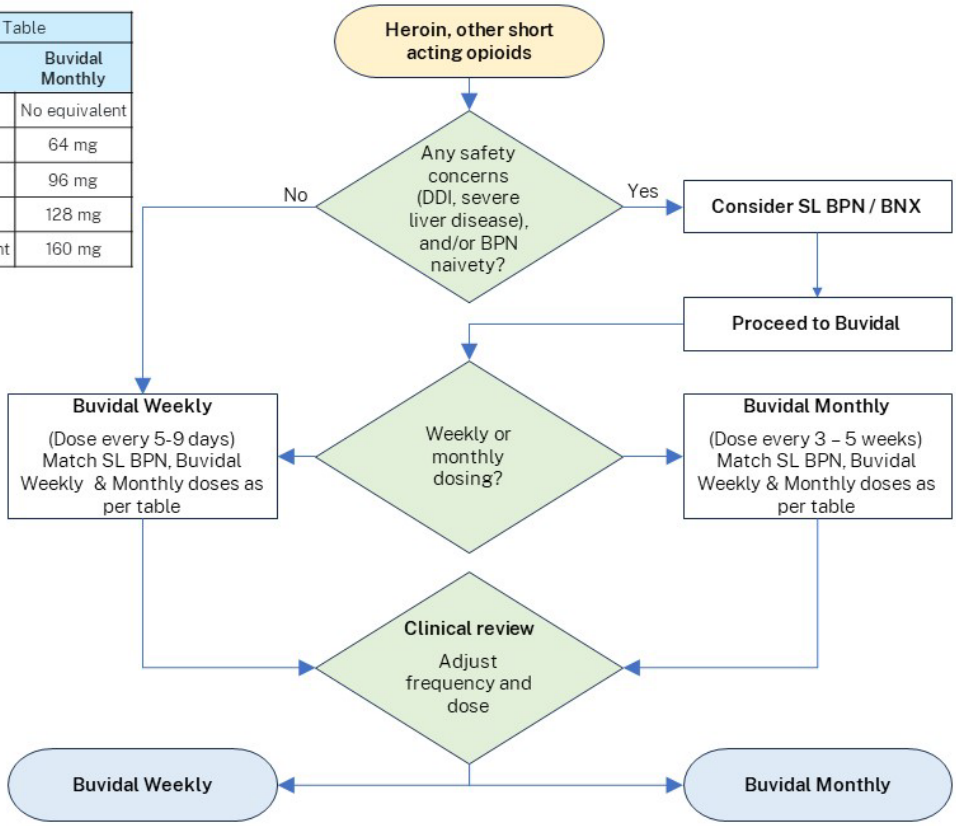
Patients may be switched from Weekly to Monthly dosing or from Monthly to Weekly dosing based on the recommendations in Table 4. Monitor patients for increased withdrawal or craving symptoms or other signs of instability. Individual titration to higher or lower doses may be required.

Whilst doses will be routinely scheduled to occur every seven (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 two days before or after the weekly time point (days five to nine), and the monthly dose may be administered 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 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 doses has elapsed, re-induction may be required, with individual clinical titration.

Figure 7. Overview of dosing with Buvidal

Dose Conversion Table		
Daily SL BPN dose	**Buvidal Weekly**	**Buvidal Monthly**
2-6 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
26-32 mg	No equivalent	160 mg



5.4 Transitioning from SL BPN treatment to Sublocade

5.4.1 Initial Sublocade doses

Sublocade treatment requires preceding treatment with SL BPN formulation for at least seven consecutive days, preferably achieving SL doses ≥8 mg daily, or after at least a seven-day period of treatment with Buvidal (see below). Longer periods of SL BPN treatment may be required prior to initiating LAIB treatment if the patient reports BPN-related adverse events or DDIs, has existing severe liver disease, or is finding it difficult to stabilise on a dose of SL BPN. There is some limited experience of safely initiating Sublocade after fewer than seven days' treatment with SL BPN (e.g. after three doses of SL BPN); however, this remains an emerging area of practice at this time [20, 21].

Sublocade can also be initiated directly for a patient who is currently on Buvidal treatment without the need for a period of SL BPN treatment. Recommendations for transferring between Buvidal and Sublocade are discussed below in section 5.7 Transfer between Buvidal and Sublocade.

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 (peak plasma levels are not achieved for 12–24 hours after the injection). The recommended dose of Sublocade for most patients upon initiation is 300 mg 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 100 mg (rather than 300 mg) doses; specifically, where there are safety concerns arising from hepatic impairment or DDIs (e.g. concomitant use of other sedatives). It is recommended under such circumstances that the decision is discussed with the patient, documented in clinical notes, and that treatment effects are regularly monitored, and the dose adjusted accordingly.

After the two initial four-week 300 mg doses of Sublocade treatment, doses are flexible with either 100 mg or 300 mg SC injections every four weeks, decided by the prescribing clinician in consultation with the patient. For many patients, 100 mg monthly Sublocade doses will be adequate, maintaining plasma levels (at steady state equilibrium) achieved with the first two 300 mg Sublocade doses, and is likely to be associated with fewer concerns regarding high-dose BPN-related adverse events. Maintenance of 300 mg doses should be considered for those patients who had previously stabilised on high-dose SL BPN (e.g. 24 mg to 32 mg daily) or continue to experience cravings or unprescribed opioid use during the first two-month period of Sublocade dosing. Clinical titration is recommended, following the principles identified in section 5.5 Key principles in titrating LAIB doses – adjusting dose and frequency of doses (CS).

5.4.2 Supplemental or 'top-up' SL BPN doses for patients on Sublocade

'Top-up' or supplemental doses of SL BPN (e.g. 4 mg or 8 mg) may be given for a limited period of time if the patient experiences clinical features of opioid withdrawal, cravings, or persistent unprescribed opioid use (see section 5.6 Supplemental BPN dosing).

5.4.3 Sublocade flexible dosing schedules and missed doses

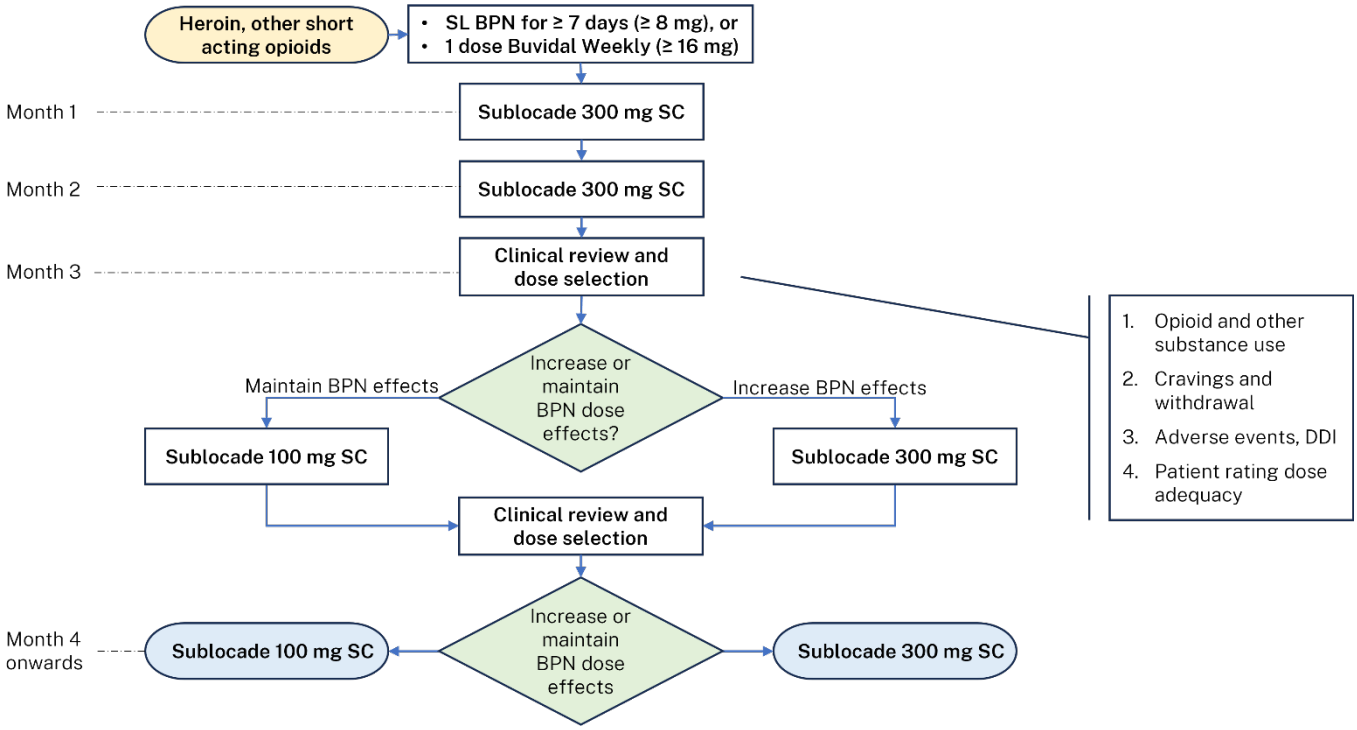
Whilst doses will be routinely scheduled to occur every 28 days, it is recognised that some flexibility is required to accommodate missed appointments, travel, public holidays, appointment availability, etc. To accommodate such scenarios, Sublocade doses can be administered up to two days ahead of a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

Once steady state has been achieved (after three 300/100 mg doses and after up to six 300/300 mg doses with Sublocade), occasional delays in dosing of up to four weeks after the last scheduled dose (i.e. up to 56 days since the last injection) 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 four weeks (i.e. more than 56 days after last injection) may be associated with reduced plasma BPN levels and caution should be exercised in re-initiating treatment with Sublocade. If there is any doubt regarding the patient's opioid tolerance (e.g. patient reports experiencing opiate withdrawal features), an assessment of withdrawal severity/duration, and a test dose of SL BPN (e.g. 8 mg) should be administered, and if there are no concerns (e.g. sedation), recommence Sublocade dosing (on the previous 100 mg or 300 mg dose) the following day.

A patient who has had no documented or confirmed BPN doses for more than 56 days after their last injection and has used heroin or other opioids regularly 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 seven or more days before recommencing Sublocade treatment. Specialist advice should be sought where prescribers require support regarding re-induction and stabilisation.

Figure 8. Overview of dosing with Sublocade



5.5 Key titration principles – adjusting dose and frequency of doses (CS)

The following is a guide to LAIB dose (Buvidal and Sublocade) selection beyond the initial doses.

In general, doses should be maintained if:

- the patient is achieving key treatment outcomes, such as no unprescribed use of opioids, no clinically significant opioid withdrawal, or cravings
- there are no clinically significant dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, nausea)
- the patient is satisfied with their current dose, and requesting the dose be maintained.

In general, doses should be reduced if:

- the patient reports BPN dose-related adverse events (e.g. sedation or lethargy, persistent headaches, nausea, elevated liver function tests associated with high-dose BPN use)
- the patient is seeking to reduce their dose in an attempt to ultimately withdraw from ODT
- the patient is reporting the dose is 'too high' and/or is seeking a dose reduction, and there are no significant concerns regarding deterioration in clinical condition (e.g. substance use, physical or mental health symptoms) that may arise with a dose reduction.

In general, doses should be increased if:

- the patient is not achieving their desired treatment goals (e.g. persistent unprescribed opioid use, opioid withdrawal symptoms, or cravings)
- the patient reports their dose is too low and they would like a dose increase, and there are no significant clinical safety concerns. Dose increases may not be advisable if the patient reports dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, constipation, nausea, elevated liver function tests). If so, alternative strategies should be considered (e.g. psychosocial approaches).

5.6 Supplemental BPN dosing

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

There may be circumstances where supplemental doses of SL BPN or LAIB are required on a short-term or interim basis until the next 'usual' LAIB dose can be administered. Examples include:

- during dose titration in the early stages of depot treatment. For example, LAIB doses are adjusted according to the patient's prior SL BPN dose. These transitional doses are a guide only, and subsequent dose adjustment may be required. Similarly, the initial Buvidal Weekly dose is recommended at 16 mg; however, this may not be sufficient to hold patients for a full seven days, and supplemental 8 mg doses may be indicated. Supplemental BPN doses may enable the patient to be held over until their next scheduled depot dose.
- following the commencement of another medication that induces hepatic metabolism of BPN. For example, a CYP3A4 inducer such as carbamazepine may cause BPN plasma levels to be reduced, resulting in features of opioid withdrawal, cravings, or unprescribed drug use.
- delayed or interrupted depot dosing. Patients may miss their routine dose of LAIB due to unforeseen circumstances such as travel, transport problems, or other commitments. In some

cases, a dose of LAIB can be organised to suit the conditions. In other cases, patients may not be able to access their routine depot dose on time. An interim period of treatment with SL BPN may be able to be organised instead, given it is more widely available in a range of community settings than the depot formulations (e.g. at a community pharmacy in a rural setting).

- in response to other stressors or deterioration in psychological wellbeing. Some patients have a history of responding to a significant stressor by using substances. Sometimes, patients may request an increase in their methadone or BPN dose 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 ODT doses under such circumstances, in practice, this can be a useful short-term measure to help patients through a difficult time, alongside working with and supporting the patient to develop alternative coping skills.

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

5.6.1 Supplemental dosing for patients treated with Buvidal

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

Where supplemental Buvidal depot injections cannot be used (e.g. no access to formulation), then additional doses of SL BPN (+/- naloxone tablets/film) may be prescribed – either to:

- add to (or 'top up') existing Buvidal (use up to 8 mg SL BPN per day); or
- 'instead of' Buvidal (in which case SL BPN doses should be guided by Table 6).

Consult with an addiction medicine specialist for further advice if required.

5.6.2 Supplemental dosing for patients treated with Sublocade

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

In circumstances of a missed Sublocade dose and where the patient is reporting features of opiate withdrawal or cravings, doses of SL BPN may be used until the next dose of Sublocade can be administered (e.g. commence with 8 mg SL BPN per day and titrate the dose accordingly on subsequent days).

There is limited experience in using 8 mg Buvidal Weekly as supplemental or top-up doses for patients routinely prescribed Sublocade. Consult with an addiction medicine specialist for advice if required.

Supplemental or top-up doses of Sublocade are not permitted.

5.7 Transfer between Buvidal and Sublocade (CS)

Transferring patients back and forth between Buvidal and Sublocade unnecessarily should be avoided.

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

- lack of availability of the formulation at a new treatment site that the patient had previously been treated with (i.e. the treatment site only has one formulation, Buvidal or Sublocade, and the patient had been treated with the other formulation)
- interrupted supply of one formulation (i.e. the formulation the patient had been treated with is not available when required)
- local injection-related adverse events (e.g. persistent pain, lumps) with one formulation
- dose adjustment. Repeated Sublocade 300 mg doses will provide higher mean daily BPN plasma levels than repeat doses of 160 mg Buvidal Monthly, and this may be a reason for a small minority of patients to change from Buvidal to Sublocade.

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 at BPN steady state equilibrium, for data on Cmax, Cmin and Cavg levels of BPN following depot administration at steady state.

5.7.1 Transfer from Sublocade to Buvidal

Patients on stable Sublocade 300 mg monthly doses should transfer to Buvidal Weekly 32 mg or Buvidal Monthly 128 mg or 160 mg. Patients may experience a decrease in serum BPN levels following transfer and may experience opiate withdrawal and/or cravings following transfer to Buvidal, although this is unlikely to occur given the long half-life of Sublocade.

Patients on steady Sublocade 100 mg monthly doses should not experience a significant decrease in serum BPN levels when transferring to Buvidal Weekly or Buvidal Monthly. Commence at 16 mg or 24 mg Buvidal Weekly or 64 mg or 96 mg Buvidal Monthly and titrate doses up or down as clinically indicated.

Table 5. Transfer between Sublocade and Buvidal

Sublocade dose	Buvidal Weekly	Buvidal Monthly
Sublocade 100 mg monthly	16 mg or 24 mg Buvidal Weekly	64 mg or 96 mg Buvidal Monthly
Sublocade 300 mg monthly	32 mg Buvidal Weekly	128 mg or 160 mg Buvidal Monthly

5.7.2 Transfer from Buvidal to Sublocade

Patients treated with only one single dose of Buvidal Weekly (induction dose), who transfer to Sublocade, should be inducted on 300 mg Sublocade doses as per routine Sublocade induction practice (for more information, see section 5.4.1 Initial Sublocade doses).

Patients who are transferring to Sublocade after an extended period of Buvidal treatment (e.g. after three or more Buvidal Monthly doses) can be transferred to 100 mg Sublocade doses or 300 mg Sublocade doses (Table 5). For patients transferring from 64 mg or 96 mg Buvidal Monthly doses, 100 mg Sublocade doses should be adequate. Patients transferring from 128 mg or 160 mg Buvidal Monthly doses may require 300 mg Sublocade doses, with subsequent clinical review and dose titration. For more information, see 5.5 Key titration principles – adjusting dose and frequency of doses (CS).

The Opioid Treatment Line (OTL) 1800 642 428
9:30am to 5:00pm, Monday to Friday (except public holidays)

A telephone helpline that provides opioid pharmacotherapy information, referrals, advice and a forum for pharmacotherapy concerns.

PeerLine 1800 644 413
Email: peerline@nuaa.org.au

A confidential peer-run telephone service providing support to people who use drugs, who are on the OTP or who are seeking treatment across NSW.

5.8 Transferring from methadone to LAIB

Treatment with LAIB is well suited to many patients; however, this treatment option is not available for many patients treated with methadone. The following indicate potential concerns in transferring patients from methadone to BPN.

5.8.1 Considerations

Precipitated withdrawal

This is experienced as a marked increase in opioid withdrawal signs and symptoms following the introduction of BPN treatment, arising from replacement of methadone (full agonist, low affinity) with BPN (partial agonist, high affinity) at mu receptors. Precipitated withdrawal is more likely to occur with:

- patients transferring from higher methadone doses (particularly higher than 60 mg, although it can occur at lower doses). This can often be mitigated by reducing the patient's methadone dose prior to transferring.
- a shorter interval between last methadone and first BPN dose. This can be partially mitigated by extending the interval until the patient is experiencing significant opiate withdrawal (e.g. COWS ≥12) before commencing BPN.
- rapid onset of high BPN plasma levels, as more methadone is displaced by higher doses of BPN. For this reason, the first day's dose of SL BPN is usually 'split' into several doses (e.g. 2 mg + 6 mg + 8 mg) rather than a single dose (e.g. 16 mg) [22].

Destabilisation and discomfort

Many patients struggle to reduce their methadone dose to low levels without destabilising their substance use, or mental or physical health. Most guidelines recommend attending to comorbid mental, physical and social conditions prior to attempting transfer; however, this can be difficult in patients not coping with methadone dose reductions.

Many patients have a period of adjustment (one to two weeks) when they do not feel their 'usual self' on BPN (often complaining of fatigue, poor sleep, anxiety), and some request to transfer back within days.

Conventional approach to transferring from methadone to SL BPN

Most clinical guidelines for transferring from methadone to SL BPN recommend patients reduce their methadone dose as far as possible (e.g. ideally to <30 mg); have a one- to four-day period between methadone and BPN doses, delaying the first BPN dose until the patient is experiencing moderate severity opioid withdrawal (e.g. COWS ≥12); and splitting the first-day SL BPN dose into small increments (e.g. commencing with 2 mg and then further doses of 4–8 mg until the patient is comfortable, often requiring 12–24 mg total dose on day one) [2, 3]. This also requires intensive activity on the first day with multiple reviews of the patient, which can be difficult to coordinate outside of specialist clinic or inpatient settings.

Transferring from higher methadone doses is often associated with greater risk of failed transfer attempt. Some patients do not complete their attempted transfer (i.e. the patient ceases the transfer attempt or returns to methadone treatment within days of the attempted transfer). This occurs infrequently (<5% of cases) when transferring from low methadone dose (e.g. <60 mg) but occurs more often (up to 20%) when attempting higher dose (>60 mg) transfers [22]. The difficulties experienced with some patients in attempting transfers has led to a search for alternative transfer strategies. This guidance describes different approaches to transferring from methadone to LAIB, some of which are described below.

Irrespective of the approach used for transferring patients, provide clear information to patients (and their support person/carer where relevant) regarding the procedures, and to have support options (e.g. after-hours telephone services) if they experience difficulties with the transfer. Frequent clinical review during and following the transfer attempt is essential. Patients should have the option of returning to methadone if they find the transfer attempt too difficult or find BPN treatment unsatisfactory (unless the transfer was undertaken due to contraindications to methadone treatment such as severe adverse events to methadone).

5.8.2 Transfer approaches

There are four ways for accredited health professionals to enable patients to transfer from methadone to BPN.

Figure 9. Overview of approaches for transferring from methadone to LAIB

			
Direct methadone to Buvidal (methadone dose ≤30 mg)	**Indirect methadone to Buvidal or Sublocade (via SL BPN) transfer**	**'Bridging' transfer (methadone dose ≥30 mg)**	**'Microdose' transfer (methadone dose ≥30 mg)**
Patients transferring from methadone doses ≤30 mg can transfer **directly** to Buvidal Weekly without microdosing or bridging medication.	**Indirect transfer** (via SL BPN) involves a standard approach for transfer from methadone to SL BPN endorsed in current NSW OTP Guidelines. Once the patient has stabilised on SL BPN for several days, transfer to LAIB can be undertaken (section 5.3).	**Bridging** with a short-acting opioid may be considered for patients on higher doses of methadone (>30 mg). Seek specialist advice if considering transfers for patients on methadone doses higher than 150 mg.	**Microdosing** (a modified 'Bernese' method) may be considered for patients on higher doses of methadone (>30 mg). Seek specialist advice if considering transfers for patients on methadone doses higher than 150 mg.
Stop methadone, monitor patient daily until in mild opioid withdrawal. Initiate Buvidal Weekly 16 mg (usually 24–72 hours after last methadone dose). Monitor patient in subsequent days, consider top-up Buvidal Weekly (8 mg) doses PRN.	Gradually reduce dose to ≤30 mg or until patient no longer tolerates dose reductions. Stop methadone, monitor patient daily until moderate-severe opioid withdrawal. Commence SL BPN, monitor and titrate SL BPN dose on subsequent days. Transfer to LAIB from SL BPN as per section 5.3.	Stop methadone. Start equivalent dose of a short-acting opioid agonist the next day (e.g. oxycodone) and continue for two to three days. Stop opioid agonist and commence Buvidal Weekly (as per section 5.2).	Maintain methadone dose whilst introducing low dose SL BPN with gradual dose increases over seven to 10 days (to at least 8 mg SL BPN daily). Monitor daily. Discontinue methadone and rapidly increase SL BPN (e.g. to 16–32mg daily) over subsequent days until patient is comfortable. Transfer to LAIB from SL BPN as per section 5.3.
For more detailed description, dosages and timing, see below.			

5.8.3 Transferring from methadone to Sublocade (indirect)

Patients seeking to transfer from methadone to Sublocade should transfer to SL BPN formulations (≥8 mg daily) for at least seven days prior to commencing Sublocade, or to Buvidal for at least seven days prior to transferring to Sublocade. Guidance on initiating SL BPN treatment from methadone can be found in the NSW OTP Guidelines and the National Guidelines for Medication-Assisted Treatment of Opioid Dependence [3] (Section A.4). Consider microdose or bridging strategies described in the appendices.

5.8.4 Transfer from methadone to Buvidal

Figure 9 outlines four methods for transferring from methadone to Buvidal. The first two approaches described are consistent with the registered product information for Buvidal. The evidence and clinical experience of the latter two approaches are still emerging, and it is recommended these are undertaken by, or in consultation with, specialist services.

The pharmacological profile of Buvidal Weekly suggests there may be advantages in using Buvidal over SL BPN doses for transfers from methadone. A key factor in the onset of precipitated withdrawal is the rapid displacement of methadone from opioid receptors with BPN. The faster the onset of BPN, the increased risk of precipitated withdrawal. Buvidal Weekly has a much slower onset of BPN plasma effects than SL doses (see Figure 2), such that precipitated withdrawal following SL dosing usually occurs within one to two hours of the first SL BPN dose, corresponding to the peak plasma levels seen with SL dosing. In contrast, the slow onset of BPN effects following a Buvidal Weekly dose (12–24 hours for peak plasma effects), suggests this should be associated with less risk of precipitated withdrawal. For this reason, the guidance below recommends avoiding 'test' doses of SL BPN when using transferring from methadone to Buvidal Weekly.

1. Direct transfer from low dose methadone (≤30 mg) to Buvidal Weekly

Patients transferring from low dose methadone (≤30 mg daily dose) can transfer directly to Buvidal Weekly doses. The recommended approach is to:

a) ensure the last methadone dose is 30 mg or less. The patient should be on low dose methadone for a period (e.g. at least several days). Avoid rapid decreases in methadone dose in this process.

b) monitor the patient daily and defer the first dose of Buvidal until the patient is experiencing mild opioid withdrawal (COWS >6, including objective signs) before initiating Buvidal Weekly dosing. This often entails initiating Buvidal 48–72 hours after the last methadone dose but can occur after 24 hours if the patient is experiencing mild opioid withdrawal. The delayed onset of Buvidal Weekly effects means that the patient does not need to be in moderate or severe opiate withdrawal (e.g. COWS ≥12) before initiating Buvidal treatment. Delaying the first Buvidal dose until the patient is in moderate or severe withdrawal (e.g. COWS ≥12) will likely result in their withdrawal not being adequately relieved for eight to 12 hours, until the BPN plasma levels increase to effective levels following the initial Buvidal dose. Emerging clinical experience suggests that the patient will have a more uncomfortable transfer process by delaying the first dose until moderate or severe withdrawal.

c) initiate 16 mg Buvidal Weekly. Avoid using SL BPN formulations prior to the first dose of Buvidal Weekly. SL BPN has a rapid onset of action (peak effects within one to two hours) and is more likely to rapidly displace methadone from receptors, compared to Buvidal Weekly, which has a much slower onset of action (first effects within one hour, but peak effects delayed until 24 hours after the last dose). Hence, the risk of precipitated withdrawal is likely to be less when initiating Buvidal Weekly than if using SL BPN doses, but is likely to occur several hours (12–24) after the first Buvidal Weekly injection (corresponding to peak BPN plasma levels).

d) monitor the patient on subsequent days, with the option of 'top-up' doses of 8 mg Buvidal Weekly (to max 32 mg in week one at 24-hour intervals).

Transfers from low dose methadone directly to Buvidal Weekly can be safely undertaken in outpatient settings; however, an inpatient admission may be indicated if there are significant concerns regarding other substance use (e.g. heavy alcohol or benzodiazepine use), mental or physical comorbidities, or unstable social conditions.

2. Indirect transfer from methadone to Buvidal treatment, via SL BPN

This approach utilises conventional guidelines for transferring from methadone initially to SL BPN, with Buvidal (Weekly or Monthly) commenced once the patient has tolerated several days of SL BPN dosing with positive outcome. Guidance on initiating SL BPN treatment from methadone can be

found in the NSW OTP Guidelines [2] and the National Guidelines for Medication-Assisted Treatment of Opioid Dependence [3] (Section A.4).

3. Transfer from methadone to LAIB using the 'bridging approach'

This approach involves transferring from methadone to Buvidal Weekly via a short duration of treatment (several days) with a short-acting opioid agonist (e.g. oxycodone, morphine) that bridges the period between methadone and BPN treatment.

For more information, see Appendix C.

4. Transfer from methadone to LAIB using the 'microdose approach'

There is emerging evidence regarding the safety and suitability of microdose techniques for transferring from methadone to BPN, modifying an approach originally described as the 'Bernese' method [23].

For more information, see Appendix C.

6. Administering LAIB injections

6.1 Administering LAIB injections

Buvidal Weekly, Buvidal Monthly and Sublocade administrations are intended for subcutaneous use only. Ensure the site chosen has sufficient subcutaneous tissue to allow for the injection. The area should be free of scarring, nodules or other lesions and should not be inflamed, infected or bruised. A steady push should be used (e.g. over 15–30 seconds). See the product information for details.

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

Practical training to administer LAIB injection is advised, as LAIB formulations have higher viscosity than many other medicines delivered subcutaneously. This could mean that the injection takes longer to administer, and that the patient may feel some discomfort or pain when the injection is administered. Refer to the product information for formulation-specific advice about administration techniques to reduce patient pain and discomfort.

6.1.1 Administering Buvidal injections

Buvidal Weekly and Buvidal Monthly should be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Injections on the waistline or within 5cm of the navel should be avoided.

Injection sites should be rotated. Rotate the injection sites between the different injection areas i.e. the buttock, thigh, abdomen, or upper arm.

The angle of injection will depend on the amount of subcutaneous tissue; however, Buvidal should usually be administered at **90 degrees**. For detailed instructions for use, refer to Appendix B.

6.1.2 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 patient in the supine position. Injection sites should be rotated. Insert needle fully into the abdominal subcutaneous tissue at an angle of 45 degrees. For detailed instructions for use, refer to Appendix B.

Sublocade must be administered at room temperature. It may take 15 minutes after removing Sublocade from refrigeration to achieve this temperature [24]. Pain associated with the injection can be reduced by placing an icepack on the injection site for 10–15 minutes before injecting.

6.2 Appropriate professionals

LAIB 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. This routinely includes nursing, medical and pharmacy professionals.

6.2.1 Medical staff

All AHPRA registered medical staff may inject LAIB, as long as they do not have any conditions or notations applied to their AHPRA registration that would prevent them administering this injection.

Contact the product manufacturers to arrange training and support. See Appendix B for contact details.

6.2.2 Nursing staff

NSW registered nurses (RNs) and enrolled nurses (ENs) in a community setting (such as a GP clinic or community pharmacy) may inject LAIB as long as:

RNs:

- do not have any conditions or notations applied to their AHPRA registration that would prevent them administering this injection

ENs:

- are under the supervision of a medical or nurse practitioner or a registered nurse (as defined by the Nursing and Midwifery Board of Australia Enrolled Nurse Standards for Practice[22])
- do not have a notation on their AHPRA registration which advises that they have not completed medication education.

Contact the product manufacturers to arrange training and support. See Appendix B for contact details.

[22] https://www.nursingmidwiferyboard.gov.au/Codes-Guidelines-Statements/Professional-standards/enrolled-nurse-standards-for-practice.aspx

6.2.3 Pharmacists

Pharmacists may administer LAIB injection in community pharmacy settings where:

1. the pharmacist holds vaccination accreditation
2. the pharmacy has a suitable consultation room to administer injections
3. the administration area and equipment complies with the NSW Pharmacist Vaccination Standards.[23]

In addition, it is essential that the formulation is supplied by a pharmacist who has dispensed the formulation for an individual patient, without ever being handled by the patient. Individual patients must never handle LAIB.

Specific accredited training is recommended for pharmacists providing this service and is available via the Pharmaceutical Society of Australia.[24]

6.3 LAIB product management outside of pharmacy settings

6.3.1 Ordering the product

Prescribers may order LAIB for a named patient via a prescription sent to a pharmacy. The prescriber should discuss this with the pharmacist before prescribing. The pharmacist must dispense the medication to the prescriber or their staff, or may deliver to the medical practice.

LAIB must never be supplied to, or collected by, a patient or their carer.

6.3.2 Storage

The usual provisions for storing Schedule 8 Drugs of Addiction apply for LAIB as outlined in the *Poisons and Therapeutic Goods Regulation 2008* (the Regulation). A summary guide[25] is available on the NSW Health website.

In settings such as medical practices, Schedule 8 drugs must be kept apart from all other goods (other than cash or documents) in a safe, cupboard, or drawer in a cabinet, which is securely attached to a part of the premises and kept locked when the drugs are not in immediate use. Emergency supplies may be carried in a bag, provided the bag is left in a locked room, locked cupboard, or locked vehicle when not in immediate use.

Buvidal

Buvidal injections are required to be stored below 25°C. Do not refrigerate or freeze. Storage requirements are set out in the relevant legislation[26] and apply as for all Schedule 8 drugs.

[23] www.health.nsw.gov.au/immunisation/Documents/pharmacist-new-standard
[24] my.psa.org.au/s/training-plan/a110o00000KYp5HAAT/nsw-longacting-injectable-BPN-administration-by-pharmacists
[25] www.health.nsw.gov.au/pharmaceutical/Documents/guide-medprac-nurse-dentist.pdf
[26] legislation.nsw.gov.au/view/whole/html/inforce/current/sl-2008-0392#pt.4-div.2

Sublocade

Store Sublocade injections refrigerated at 2–8°C. Do not freeze.

Advice about storage of a Schedule 8 medicine requiring refrigeration[27] is available on the NSW Health website.

Sublocade can be removed from the fridge and kept at room temperature (<25°C) for up to 12 weeks* prior to use.

Store in original packaging and discard if unused after 12 consecutive weeks* out of the fridge. Clinicians who do not have secure refrigerated storage may order the product within 12 weeks of intended use to avoid the need for refrigerated storage.

Once outside the refrigerator, this product must continue to be stored according to the requirements of Division 2 Part 4 of the Regulation for Schedule 8 drugs. Once Sublocade has been removed from cold storage, it should not be put back into cold storage.

Sublocade should be removed from cold storage for at least 15 minutes prior to administration to allow passive warming to room temperature.

***Extended ambient shelf life Sublocade has been available in Australia since April 2024**, following a change to new oxygen-absorbing desiccant. Some older stock will have a shorter room temperature shelf life and may only be stored at room temperature for 28 days.

Please refer to the information on the pack for the correct storage conditions.

[27] www.health.nsw.gov.au/pharmaceutical/Pages/refrigeration-s8s.aspx

7. Discontinuing LAIB treatment

Potential reasons for discontinuing LAIB treatment are:

- a goal of opioid abstinence
- transfer to SL BPN
- transfer to methadone or other opioid analgesics
- transfer to oral naltrexone.

7.1 Withdrawing from LAIB (with the goal of opioid abstinence)

Many patients on ODT are keen to achieve abstinence, discontinue opioid treatment, and withdraw from opioids. Most patients attempting withdrawal from ODT relapse to unprescribed opioid use and are at increased risk of opioid overdose; 10–20% of patients ceasing ODT achieve complete opioid abstinence in the short to medium term [25–27].

Whilst some patients describe withdrawal from SL BPN treatment as ‘shorter’ and ‘easier’ than methadone withdrawal, there is little evidence to indicate better longer-term success rates with either medication [28]. A better prognosis for successful withdrawal from ODT is achieved for patients who:

- have been able to stop using non-prescribed opioids
- do not have other significant substance use problems – who have been able to make lifestyle changes to support ongoing cessation of opioid use (e.g. employment, education, supportive relationships)
- have gradual rather than precipitous reduction regimens on methadone or BPN.

These conditions are most likely also relevant for patients attempting withdrawal from LAIB treatment.

There is increasing clinical experience regarding withdrawal from LAIB treatment, although few published reports [29, 30]. The onset, peak, and duration of withdrawal symptoms are likely to vary

between patients. These may be affected by the duration of prior LAIB dosing (with a slower reduction in plasma levels following long-term LAIB treatment); the last dose of LAIB administered withdrawal (likely to be more severe if stopping higher dose LAIB); and individual variation in pharmacokinetics.

Whilst the withdrawal time course and severity has not been clearly characterised for the LAIB formulations, early clinical experience suggests that opioid withdrawal syndrome on stopping LAIB may be of lower severity than withdrawal from stopping SL BPN, and that withdrawal syndrome from LAIB occurs as plasma levels from LAIB subside following the last dose. Table 6 below highlights the likely timeframe at which most patients are likely to experience an opiate withdrawal syndrome following discontinuation of LAIB treatment – usually within two to five half-lives of the medication. Expect considerable individual variability. Patients should be educated about the possible timeframe and variation in the onset, severity, and timeframe for withdrawal symptoms when discontinuing depot BPN, in particular differences from SL BPN in the withdrawal syndrome.

Table 6. Timeframe for likely withdrawal syndrome following LAIB discontinuation

LAIB	Half-life (at repeated doses)	Likely timeframe for onset and peak withdrawal symptoms after last maintenance depot dose
Sublocade 300 mg doses	43–60 days	8–24 weeks after last dose
Sublocade 100 mg doses	43–60 days	8–24 weeks after last dose
Buvidal Weekly	3–5 days	1–3 weeks after last dose
Buvidal Monthly	19–25 days	6–12 weeks after last dose

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

- for patients on Buvidal Weekly, reducing to the 8 mg weekly dose before ceasing LAIB
- for patients on Buvidal Monthly, reducing to the 64 mg dose before ceasing LAIB
- for patients on Sublocade, reducing to the 100 mg dose before ceasing LAIB.

As with attempts to withdraw from other forms of ODT, patients (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 (National Guidelines for Medication-Assisted Treatment of Opioid Dependence [3] Section A.4); however, caution should be exercised in extended use (beyond a few days) of sedatives or hypnotic medications. Patients who have withdrawn from LAIB should be strongly encouraged to access supplies of THN to reduce the risk of overdose if the patient resumes opioid use.

The severity and duration of withdrawal symptoms are only one factor in influencing resumption of unprescribed opioid use, and despite the likelihood that withdrawal severity from LAIB may be milder than withdrawal from SL BPN or methadone, clinicians and patients should prepare for relapse and have management plans to minimise resumption of substance use including psychosocial supports, THN for overdose prevention, resumption of ODT, or other alcohol and other drugs (AOD) treatment.

7.2 Transfers to SL BPN (CS)

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

7.2.1 Sublocade to SL BPN

Recommended practice is to initiate SL BPN with low doses at approximately the time of the next scheduled LAIB injection – usually commencing with 8 mg SL BPN four weeks after the last Sublocade dose. Titrate the dose upwards over subsequent days or weeks according to clinical need (such as features of withdrawal, craving, intoxication, use of unprescribed drugs) as the LAIB concentrations gradually subside.

Whilst there are no published dose conversion tables between Sublocade and SL BPN, patients on 300 mg Sublocade are likely to ultimately require doses of 24–32 mg SL BPN daily, whereas patients on 100 mg Sublocade may stabilise longer term on lower doses (8–24 mg). Frequent clinical review and dose titration are recommended.

7.2.2 Buvidal to SL BPN

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

Patients should be reviewed regularly, and doses titrated according to clinical need. Clinicians are required to document the rationale for their decision-making.

Table 7. Dose conversion: Buvidal Weekly and Buvidal Monthly to SL BPN

Buvidal Weekly depot dose	Buvidal Monthly depot dose	Daily SL BPN dose
8 mg		2–6 mg
16 mg	64 mg	8–10 mg
24 mg	96 mg	12–16 mg
32 mg	128 mg	18–24 mg
	160 mg	24–32 mg

7.3 Transfer to methadone or other opioid analgesics (CS)

Clinical experience regarding transfer from LAIB to methadone or other opioid agonists (e.g. morphine, oxycodone) is emerging. When transferring from LAIB to full opioid agonists (e.g. methadone), it is important to recognise that 'residual' BPN from LAIB doses may be present for weeks or months after long-term treatment with monthly LAIB formulations. This residual BPN may block or reduce the effects of methadone (or other agonist) doses. As such, patients require frequent clinical review over subsequent weeks as BPN plasma levels subside, which may impact on the effects of methadone (or other agonists).

Patients seeking to transfer from LAIB to methadone can either:

- transition LAIB to SL BPN and then to methadone (as described in the NSW OTP Guidelines [2]
- transition directly from LAIB to methadone. The general principle is to recommence low dose methadone (e.g. 20–40 mg oral daily doses) at the time of the next proposed LAIB dose. Lower methadone doses (e.g. 20–30 mg) may be appropriate for patients transferring from 100 mg Sublocade or 64–96 mg Buvidal Monthly, whereas higher doses (30–40 mg) may be appropriate for patients transferring from 300 mg Sublocade or 128–160 mg Buvidal Monthly. Regularly monitor the patient (at least weekly), and carefully increase the dose in subsequent days and weeks (by no more than 5–10 mg intervals) until the methadone dose has stabilised and the patient is comfortable. It is likely that patients may take several weeks to reach their maintenance dose of methadone.

Note that only accredited OTP prescribers may undertake initiation of methadone (including transfer).

7.4 Transfer to oral naltrexone (CS)

There is limited experience in transitioning from LAIB to naltrexone. In general, the initiation of naltrexone treatment has the potential to precipitate withdrawal in people using opioids (including BPN), and as such, commencement of naltrexone is usually deferred until the patient has stopped using full opioid agonists for at least seven days, and between one and five days after last SL BPN dose. Extrapolating to LAIB, initiation with oral naltrexone may be considered as BPN plasma levels subside, at least seven days after the last Buvidal Weekly dose, and at least four to six weeks after the last Buvidal Monthly dose, and six to eight weeks after last Sublocade dose. The risk of precipitated withdrawal under these circumstances is considerable, and transfer should generally be undertaken in an inpatient setting or under close observation, following a urine drug test negative for opioids, and consider the role of a naloxone challenge test. Low naltrexone doses should be initiated (e.g. 12.5 mg daily), increasing by 12.5 mg per day until the target dose of 50 mg daily is achieved.

Given the lack of experience in transferring from LAIB to naltrexone, consultation with an addiction medicine specialist and close clinical monitoring is recommended.

8. Clinical conditions

8.1 Acute pain management in patients in LAIB treatment

Patients on ODT frequently encounter episodes of acute pain that require management. BPN treatment may complicate pain management. Nevertheless, there are approaches for successful acute pain management in patients in BPN treatment.

Non-opioid medications (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol) and physical therapies (e.g. acupuncture, transcutaneous electrical nerve stimulation [TENS]) are recommended for the management of mild acute pain.

The management of moderate or severe acute pain (e.g. in acute/emergency situations such as trauma, renal stones) may require the use of opioid analgesia. BPN can complicate routine opioid analgesia in the management of moderate to severe acute pain, with patients in BPN treatment likely to require high doses of opioids to achieve effective analgesia, as:

- BPN has high mu-receptor affinity and reduces the effects (particularly at high BPN doses) of most full opioid agonists such as morphine or oxycodone
- patients with long term opioid dependence may have opioid hyperalgesia, making them more sensitive to painful stimuli than people without regular opioid use
- patients treated with BPN have opioid tolerance, requiring higher doses of opioids to achieve the desired effect than people not using opioids regularly.

Two recent reviews [31, 32] examining perioperative pain management in patients treated with SL BPN arrived at similar recommendations. Both groups of authors recommend:

1. *continuation of BPN treatment* – either at full dose [31] or at a reduced dose (8 mg daily [32]). This was considered preferable to ceasing BPN (and treating with full opioid agonists alone) due to the need for lower total opioid agonist doses and better coordination of ODT on release from hospital.
2. *addition of full agonist opioid analgesics titrated to clinical effect* – often requiring higher than usual doses to achieve analgesia. Education of patient and hospital staff regarding the need for higher doses of opioids can support hospital staff to better understand the patient experience and avoid stigmatising the patient as ‘drug-seeking’.
3. *addition of multimodal pain strategies* – including other medications (e.g. ketamine, clonidine, dexmedetomidine, NSAIDs, paracetamol), and physical and psychological therapies.
4. *coordination with community ODT providers for transfer of care and pain management strategies.*

Given the difficulty in abruptly discontinuing BPN in patients treated with LAIB, a similar approach is recommended for managing moderate-severe acute pain in patients treated with LAIB. Surgical excision of LAIB is not normally recommended. In the exceptional clinical circumstance that requires discontinuing BPN, it is crucial to ensure that the patient does not experience withdrawal symptoms and the subsequent heightened pain due to their established BPN tolerance. A collaborative discussion involving both the primary medical team and the acute pain team is strongly recommended.

Consider the legislative requirements for approval to prescribe other opioid analgesic agents when treatment is intended for outpatient care, and who will manage that period of treatment.

8.2 Chronic pain management in patients in LAIB treatment

Chronic pain is common amongst patients on ODT (estimated at 30–60% of patients) and is often managed or 'masked' by the high doses of methadone or BPN used to treat opioid dependence. Whilst current evidence does not identify the most effective strategies for treating chronic pain in patients in methadone or BPN treatment, general principles of chronic pain management should be followed [33], as well as patient education and engagement in the treatment process, appropriate use of opioid and non-opioid medications (e.g. antidepressants, NSAIDs, paracetamol, gabapentinoids), and physical (e.g. exercise, physiotherapy) and psychosocial (e.g. cognitive behavioural therapy) interventions.

BPN itself is a powerful opioid analgesic that is widely used in chronic pain management. Low dose BPN formulations (tablets and extended release seven-day topical patches) are indicated for chronic pain management, and there is increasing experience in the use of high dose BPN formulations in patients with combined chronic pain and opioid dependence. The potential benefits of high dose BPN in chronic pain treatment include the enhanced safety of BPN compared to other opioids (less respiratory depression, overdose, mortality, and fewer adverse effects); the ability to use it across a broad patient spectrum (drug clearance does not change with age, renal impairment, or mild hepatic impairment); and BPN is associated with less opioid hyperalgesia compared to many other mu-opioid receptor agonists. Concerns regarding limited analgesic potential due to the 'ceiling effects' of BPN have proven to not be founded [34].

To date, most experience in using BPN to treat patients with chronic pain and opioid dependence is with the use of high dose SL BPN formulations. A systematic review identified rotation to high dose BPN from other opioids in patients with pain resulted in comparable or improved pain outcomes compared with treatment with mu-opioid receptor full agonists, and considerably better outcomes than opioid taper and discontinuation [35]. Clinical experience [24, 36, 37] suggests most patients treated for combined chronic pain and opioid dependence require high SL BPN daily doses (e.g. commonly >16 mg daily), and that pain outcomes may be improved with split daily dosing rather than single-day dosing.

Whilst BPN treatment can be an effective element of treatment, a comprehensive treatment plan should address non-opioid medication (e.g. role of NSAIDs, gabapentinoids, antidepressants, paracetamol) and include non-medication strategies (psychological and physical therapies).

To date, there is limited published evidence regarding LAIB in chronic pain management. Theoretically, there may be advantages in using LAIB over SL BPN in the treatment of patients with chronic pain and opioid dependence due to its prolonged duration of action (with less potential for breakthrough pain during trough levels of SL BPN), continuous release over extended periods of time (compared to daily dosing of SL BPN), and the behavioural implications of separating the link between 'taking a tablet' and 'onset of pain' that is experienced by many patients using opioid medications. Further research is required in this area before clinical recommendations can be made.

8.3 Polydrug use and regular intoxication

Specific interventions may be required for patients with harmful patterns of other substance use – such as alcohol, benzodiazepine, stimulants, cannabis, and/or injecting drug use. These are described in the NSW OTP Guidelines [2]. Patients with patterns of regular and harmful substance use often benefit from regular clinical monitoring and review, which may be more difficult to schedule in patients attending for dosing only once a month.

If more frequent clinical reviews are required and the patient has a history of non-attendance for scheduled appointments and LAIB doses, then a medication option with a more frequent dosing interval (e.g. Buvidal Weekly, or daily SL BPN) may be considered. Patients with heavy and regular/dependent patterns of use of alcohol, benzodiazepines and/or 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.

8.3.1 Managing risks from concomitant use of benzodiazepines or other CNS depressants

LAIB provides higher average blood levels over a weekly or monthly period compared to the daily changes in BPN blood levels with SL BPN (see Chapter 3: Clinical pharmacology). Concomitant use of BPN with CNS sedatives (e.g. alcohol, benzodiazepines, TCAs, gabapentinoids, and antipsychotic medications) increases the risk of overdose, respiratory depression, and death. It remains unclear whether these risks are increased or reduced with LAIB compared with SL BPN treatments.

Management options include the stabilisation, reduction, or cessation of benzodiazepines or other CNS depressants (usually through a monitored and gradual taper [3], or decreasing the doses of other sedative medications to the lowest effective dose). Alternative medications and non-pharmacologic treatments for anxiety or insomnia should be considered. Ensure that other healthcare providers are aware of the patient's BPN treatment.

Important risk mitigation approaches include:

- consumer education regarding the risks of polysubstance use (including the use of prescribed sedating medication)
- cautions regarding driving or operating machinery under such conditions
- the provision of THN intervention
- frequent monitoring and review of the patient, and examining individual patient treatment goals.

Refer to Appendix A for DDIs.

8.3.2 Intoxicated presentations

Assess patients who present intoxicated at the time of dose administration to identify any safety concerns regarding dosing.

Peak plasma and clinical effects occur approximately 12–24 hours after Buvidal Weekly depot injections, 6–10 hours after Buvidal Monthly and 24 hours after a Sublocade injection. This differs from intoxicated presentations for SL BPN or methadone dosing, where peak medication effects (usually 60–90 minutes after dosing) are likely to occur whilst the patient is still intoxicated.

There is usually not a clinical indication to withhold a LAIB injection due to a patient presenting intoxicated, as the period of intoxication will have passed before the peak in BPN effects occurs

following LAIB injection. However, the risk of ongoing substance use by the patient (e.g. following a dose of LAIB) should be considered.

Intoxicated patients should be assessed for the capacity to provide informed consent to their usual dose, and to understand warnings regarding risks of sedation and overdose from polysubstance use. If there are concerns that the patient is very intoxicated and unable to understand or follow instructions, or there is considerable risk that the patient will continue to use other substances, the administration of the dose may be deferred and rescheduled.

Consultation with an addiction medicine specialist is advised if there are concerns regarding dosing.

8.4 Overdose

Whilst BPN on its own is rarely associated with overdose in people with tolerance to opioids, overdose can occur in the context of polydrug use, specifically the use of other sedatives such as alcohol, benzodiazepines, sedating antipsychotics and antidepressant medications. 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. 10 mg 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. 1–2 mg IM/IV).

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

8.5 Liver disease

Moderate or severe hepatic impairment (Child-Pugh B or C) slows down hepatic metabolism of BPN, resulting in higher plasma levels (estimated at 1.6 times greater in Child-Pugh B, 2.8 times greater in Child-Pugh C) [20] 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 LAIB has not been studied. Due to the long-acting nature of the formulation, adjustments to LAIB dosages are not rapidly reflected in plasma BPN levels. Because BPN levels cannot be rapidly decreased or adjusted, LAIB should be used with caution in patients with pre-existing severe hepatic impairment (e.g. Child-Pugh B or C) until the impact of long-term BPN treatment on hepatic function (using SL BPN) is ascertained.

An assessment of hepatic function (including clinical examination and liver function tests) prior to treatment initiation with LAIB is recommended if there are any concerns regarding pre-existing liver disease (e.g. viral hepatitis, alcohol use disorder). Where a patient is identified as having clinically relevant liver disease (more than a mild elevation of liver function tests), 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 LAIB treatment.

Lower initial LAIB dosing schedule (e.g. Buvidal 8–16 mg weekly, 64 mg monthly or Sublocade 100 mg monthly injections) should be considered for patients with significant hepatic impairment. Regular monitoring of liver function should occur for patients with persistent and severe liver disease whilst being treated with LAIB (e.g. clinical examination, liver function tests two to four weeks early in treatment, and at three- to six-month intervals once stabilised), and underlying causes (e.g. viral hepatitis, alcohol use) should be addressed. Patients who develop moderate to severe hepatic impairment while being treated with LAIB 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 300 mg, Buvidal 160 mg), and patients should be warned accordingly. Termination of LAIB treatment may be warranted if a patient's hepatic function significantly deteriorates. Specialist consultation is recommended. In one case, surgical removal of the Sublocade depot was followed by improvement in liver enzymes (see Appendix B – Sublocade product information).

8.6 Surgical removal of LAIB

Data on surgical removal of Buvidal is not available.

In the event the depot Sublocade dose must be removed, it can be surgically excised under local anaesthesia within 14 days of injection. Only the most recently injected depot can be removed.

The surgical procedure requires a small incision in the abdomen where the depot was placed, removal of the depot with forceps, and suturing to close the incision. The removed depot should be handled with adequate security, accountability, and proper disposal, according to facility procedure for a Schedule 8 drug formulation and pharmaceutical biohazardous waste, and per applicable regulations.

The residual plasma concentrations from previous injections will decrease gradually over subsequent months. Patients who have the depot removed should be monitored for signs and symptoms of withdrawal and treated appropriately [12].

9. Use of LAIB for withdrawal treatment

9.1 Use of LAIB for treatment of withdrawal

There is considerable interest among patients and clinicians in the use of long-acting depot BPN formulations to assist in withdrawal from opioids such as heroin.

Theoretically, LAIB formulations should provide a safe and effective medication to assist the management of heroin withdrawal. LAIB has a long duration of action, provides gradual taper of BPN plasma levels, and may be logistically easy to deliver and integrate in a withdrawal treatment episode (e.g. one single dose at the beginning of the withdrawal episode, without need for subsequent daily dosing). The gradual taper over days (for Buvidal Weekly) or weeks (Buvidal Monthly, Sublocade) may be well suited to assisting patients in their attempts at opiate withdrawal.

There is currently little evidence or experience in using LAIB to assist the management of heroin withdrawal, and whilst there are emerging case reports in the literature, further research is required to establish the role of LAIB for treating withdrawal from heroin or other short-acting opioid agonists. Anecdotal reports suggest a single dose of Buvidal (e.g. Weekly 16 mg) or Sublocade dose can provide effective relief of opioid withdrawal symptoms in patients stopping regular heroin use [2]. Consultation with an addiction medicine specialist is recommended.

Withdrawal treatment can easily change into longer-term or maintenance treatment when using BPN formulations (including LAIB). Given the high rates of relapse (and increased overdose risk) following short-term withdrawal treatment, longer-term use of LAIB may be considered a successful outcome.

10. Priority populations and special settings

10.1 People facing greater barriers to treatment access

There are a range of health conditions, social circumstances, and demographic backgrounds that can greatly impact upon the experience of, and access to, ODT. These are not unique to LAIB, but the less frequent dosing of LAIB may impact upon how patients engage with treatment. Important factors to consider include:

- paying particular attention to informed consent to treatment with LAIB formulations
- facilitating access to consumer workers or advocacy services
- understanding that an unintended consequence of less frequent dosing may be a reduction in opportunistic access to other treatment and services.
- collaboratively planning and implementing strategies with patients that enhance attendance for dosing and clinical reviews. Active follow-up strategies should be put in place for patients who do not attend scheduled appointments.

See below for examples of people who face greater barriers to treatment access.

People living with	People experiencing	People who are
• cognitive impairment • severe psychiatric and/or physical health conditions • disability • chronic pain	• financial concerns • child protection concerns • domestic and family violence • insecure housing • low levels of literacy • social isolation • custody • hospitalisation	• Aboriginal and Torres Strait Islander • from culturally and linguistically diverse backgrounds and communities • women • LGBTQIA+ • older • younger • living in regional or rural areas

10.2 Aboriginal and Torres Strait Islander people

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

Existing mainstream models of practice in the AOD field have been developed primarily within systems of knowledge across western cultures, and may ignore an Aboriginal and/or Torres Strait Islander perspective. Application of these models to working with Aboriginal and Torres Strait Islander people can be detrimental and undermine cultural ways of working. This can affect engagement with, and experience of, the health system and impact on decisions to seek support and treatment.

Models of AOD treatment, which are framed from within an Aboriginal and Torres Strait Islander cultural context and developed by Aboriginal and Torres Strait Islander people, are likely more effective for their treatment. These models respect the rights, values, and expectations of Aboriginal and Torres Strait Islander people, and acknowledge the diversity within and between communities living in remote, regional, and metropolitan areas.

These models:

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

A range of resources are available[28] to support shared decision-making between clinicians and Aboriginal and Torres Strait Islander people.

10.3 Hospital and custodial settings

Many patients on ODT 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 anticipated this will be less of a concern with LAIB treatment. Careful coordination between hospital and correctional staff with LAIB treatment providers is still required.

LAIB has several potential benefits as a treatment option in the custodial setting, including:

- reduced capacity for diversion and associated non-medical use, interpersonal violence, and injecting-related injuries and diseases
- reduced demand on custodial and health staff time for dosing (compared to daily BPN or methadone treatment)
- enhanced stability and continuity of care upon release (a period of high risk of overdose). The longer dosing windows for LAIB removes the need for patients to attend for ODT dosing the day after release when there are often geographic, housing, social, and financial barriers to overcome [38].

Due to reduced frequency of dosing and related reduced demand for correctional and health staff time, the resource requirements for LAIB treatment are less than for SL BPN and methadone treatment [39].

In NSW, at the time of publication of these guidelines, SL BPN is not routinely offered in custodial settings unless a patient has contraindications to the use of LAIB. Patients entering custody on methadone continue treatment with methadone, but patients entering custody on SL BPN are given the option of transferring to LAIB or ceasing ODT. Patients commencing treatment in custody are typically offered LAIB only.

When patients leave custodial settings on LAIB, re-assessment and review in their community treatment setting should include discussing their treatment options. Some patients may request transfer to SL BPN or methadone if this was not possible for them to access during their time in custody.

Patients on LAIB leaving custody should be provided education about the persistent clinical effects of LAIB. As LAIB 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 several months pre-release.

10.4 Residential rehabilitation and supported housing settings

AOD residential rehabilitation services and residential care services (e.g. nursing homes) have been limited in their capacity to support patients prescribed methadone or SL BPN due to dispensing and storage requirements of takeaway doses. LAIB provides an opportunity to better integrate ODT across these residential settings.

[28] aci.health.nsw.gov.au/shared-decision-making

To obtain advice about which services can accommodate LAIB treatment, contact the:

Opioid Treatment Line (OTL)
1800 642 428
9:30am to 5:00pm
Monday to Friday (except public holidays)

10.5 Managing travel

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

See the NSW Opioid Treatment Program webpage for information on travel regulatory requirements.

10.5.1 Local travel

The duration of action of LAIB should make local travel less problematic for patients. For information on doses that need to be given before and after the scheduled date, see sections 5.3.3 Buvidal flexible dosing schedules and missed doses and 5.4.3 Sublocade flexible dosing schedules and missed doses.

10.5.2 Interstate transfer

For more information about interstate transfers, see the NSW OTP Guidelines, section 3.5 Prescriber-related information. Beyond interstate sites having access to Buvidal and/or Sublocade, there are no additional requirements.

Whilst a medical practitioner or nurse practitioner prescribing under another jurisdiction is not subject to NSW laws, there are procedures in NSW to optimise patient safety.

Interstate prescribers who wish to temporarily transfer a patient to the NSW OTP are required to complete and submit an Application for Temporary Interstate Transfer to NSW Opioid Treatment Program.[29]

For information about permanently transferring an OTP patient to NSW or temporarily transferring a NSW OTP patient to another state/territory, refer to NSW Opioid Treatment Program website.

To optimise patient safety, access to the prescribing practitioner's jurisdictional Real Time Prescription Monitoring (RTPM) database should be sought.

10.5.3 Overseas travel

As Buvidal and Sublocade cannot be given to patients, overseas travel will require transferring patients back to SL treatment if the travel duration is more than the interval between LAIB doses. Dose titration of the required SL dose should occur before travel commences so patients can be observed during transfer from LAIB to SL BPN.

[29] www.health.nsw.gov.au/pharmaceutical/Documents/OTP-interstate.pdf

Contact the manufacturers to obtain up-to-date information about the registration status and availability of products overseas. At the time of writing, Sublocade is registered and available in the United States (US), and Buvidal is registered and available in many countries in the European Union (EU) and the US (under the trade name 'Brixadi').

11. Pregnancy, breastfeeding, and contraception

11.1 Principles for the care of patients who are pregnant

Patients should be involved in decision-making regarding their treatment.

ODT treatment is first line treatment for opioid dependence during pregnancy.

Optimal antenatal care for pregnant women who are on ODT includes regular liaison between their ODT team and antenatal 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 baby.

Adequately document discussions and outcome decisions in the patient file.

11.2 Overview

SL BPN and LAIB can be prescribed during pregnancy and breastfeeding. BPN is listed by the TGA as a Pregnancy Category C medication. SL BPN should be considered as the first line agent for women with opioid dependence not already on ODT [40, 41]. BPN is a first line treatment alongside methadone for ODT in pregnancy [2, 33, 40, 42]. Systematic reviews show that the efficacy and safety of SL BPN treatment during pregnancy is similar to methadone.

BPN and methadone treatment, provided with adequate antenatal care, are associated with retention in treatment, reduced maternal heroin/other opioid use, reduced fetal death, increased neonatal birth weight, and decreased premature delivery [33, 40].

Switching from methadone to BPN is not routinely recommended in pregnancy due to the risk of precipitated withdrawal. If this needs to occur, specialist addiction medicine advice is recommended.

Whilst there is robust data on the safety and effectiveness of SL BPN in pregnancy, there is a paucity of data on the safety and effectiveness of LAIB formulations in pregnancy and breastfeeding.

While BPN is the principal component of LAIB, two main differences exist compared to SL BPN:

- overall higher and more stable maternal blood levels of BPN than typically seen with SL BPN treatment
- excipients in Buvidal Weekly, Buvidal Monthly, and Sublocade for modified release.

The individual risks and benefits of continuing any medication, and alternate medication options, should be considered during pregnancy. After discussion of risks and benefits of continuing/changing treatment, pregnant women treated with LAIB may choose to be transferred to SL BPN, noting the substantial data on the safety and effectiveness of SL BPN in pregnancy. Informed consent is required.

There may be clinical situations where pregnant women may not easily transfer to SL BPN (e.g. lack of access to daily SL treatment dosing) or it may be considered that a pregnant woman is more likely to remain stable on LAIB rather than transferring to SL treatment (i.e. the risks of transfer to SL treatment may outweigh the expected benefits). A principle of opioid treatment in pregnancy is not changing treatment if this can be avoided [43].

LAIB should be used during pregnancy if the potential benefits outweigh the potential risks to the mother and baby. Consider section 11.1 Principles for the care of patients who are pregnant to continue LAIB during pregnancy. For women who have not stabilised on SL BPN, it may be appropriate to trial LAIB during pregnancy after a risk–benefit discussion.

11.2.1 BPN excipients

Consideration of the excipients in different BPN formulations may inform the risk–benefit discussion.

Table 8. BPN excipients in Buvidal Weekly, Buvidal Monthly, and Sublocade

Excipient	Buvidal Weekly	Buvidal Monthly	Sublocade
Soybean phosphatidylcholine	Yes	Yes	
Glyceryl dioleate	Yes	Yes	
Anhydrous alcohol	15–62 mg		
N-methyl-2-pyrrolidone		57–142 mg	278–833 mg
Poly(D,L-lactide-*co*-glycolide)			Yes

N-methyl-2-pyrrolidone (NMP) is an excipient in Buvidal Monthly and Sublocade. NMP is likely to cross the human placenta. Buvidal Weekly does not contain NMP.

Whilst there is preclinical evidence of a dose-dependent NMP toxicity [44], and a single human case study of stillbirth in the late 1990s with very high dose NMP exposure, a causal relationship was not established in that exposure [45–47]. NMP doses in Buvidal Monthly and Sublocade are less than the threshold for listing as a chemical for caution (Schedule 5) or poison (Schedule 6) in the current 2024 Australian Standard for the Uniform Scheduling of Medicines and Poisons [48]. There is evidence of population widespread NMP exposure in Europe [49], not exceeding human biomonitoring guidance values.

For more information about the care of patients through pregnancy, breastfeeding and the postnatal period, see Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period.[30]

11.3 Buvidal

Pregnancy and breastfeeding are not contraindications to use of Buvidal Weekly and Buvidal Monthly [2, 4]. See Appendix B for Buvidal product information.

Buvidal Weekly contains BPN and phosphatidylcholine (from soybean), glyceryl dioleate, and anhydrous alcohol. Soybean phosphatidylcholine is a refined lipid formulation that can contain traces of soya protein. Phosphatidylcholine has been suggested as a supplement during pregnancy [50]. Hypersensitivity to soybean-produced products is a known, but very rare, adverse event in the general population [31]. Glyceryl dioleate occurs naturally in human plasma.

The maximum level of ethanol in Buvidal (weekly formulation, 32 mg) is <100 mg per dose (note one standard alcohol drink = 10 g of ethanol). According to EU regulations, <100 mg ethanol is not considered a concern for ‘pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy’ [32, 51].

[30] www.health.nsw.gov.au/aod/professionals/Pages/substance-use-during-pregnancy-guidelines.aspx

Buvidal Monthly contains BPN and soybean phosphatidylcholine, glyceryl dioleate and NMP. For the amounts of NMP in Buvidal Monthly, see Table 8: BPN excipients in Buvidal Weekly, Buvidal Monthly, and Sublocade.

11.4 Sublocade

Pregnancy and breastfeeding are not contraindications to the use of Sublocade. See Appendix B for Sublocade product information.

Sublocade contains BPN and NMP and poly(D,L-lactide-*co*-glycolide) (PLGA/polyglactin). PLGA is a biodegradable polymer with a high molecular weight that is unlikely to cross the maternal/fetal placental barrier with minimal associated toxicity and is approved by the FDA and EMA in drug delivery systems in humans [52]. There are no current concerns regards PLGA exposure during pregnancy in preclinical models [53, 54]. For the amounts of NMP in Sublocade see Table 8: BPN excipients in Buvidal Weekly, Buvidal Monthly, and Sublocade. The US Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Improvement Protocol 63 recommends that 'women should be advised that the use of Sublocade during pregnancy should be considered only if the benefits outweigh the risks' [55].

11.5 Neonatal withdrawal

Neonatal opioid withdrawal syndrome (NOWS) is an expected and, if not treated, potentially life-threatening outcome of prolonged opioid exposure during pregnancy. Whilst BPN, like methadone, is associated with a risk of NOWS, the benefits of opioid agonist treatment are well established in pregnancy [40, 58].

There is a lack of data on the risks of NOWS when pregnant women have been treated with LAIB, compared to SL BPN. LAIB may be associated with a reduced risk of NOWS due to reduced differences in peak to trough BPN levels and lower nor-BPN levels and therefore may be a preferred medication in pregnancy [57]. Advise pregnant women receiving opioid treatment with LAIB there is a risk of NOWS and ensure that appropriate neonatal treatment will be available, noting that the onset and duration of NOWS may be longer with the long-acting injectable formulation (e.g. 24 to 48 hours after expected onset with SL BPN).

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

11.6 Breastfeeding

Pregnancy and breastfeeding are not contraindications to Buvidal Weekly, Buvidal Monthly, or Sublocade in the Australian product information [10–12]. Average serum levels of BPN seen with LAIB treatment may be higher than seen with SL BPN treatment (see section 3.2 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 [58], the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LAIB treatment alongside any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

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

LAIB should be used during breastfeeding if the potential benefits outweigh the potential risks to the mother and baby.

11.7 Contraception

Opioid treatment can alter fertility, as can changes in substance use, nutrition, mental health, and other health conditions. Women on ODT treatment should be provided with advice regarding contraception as part of routine care when commencing opioid treatment, and on an ongoing basis during treatment. Long-acting reversible contraception, such as levonorgestrel IUD (Mirena), etonogestrel implant (Implanon), or progesterone depot injections (Depo-Provera), are recommended for women who use AOD [59]. Further advice about contraception can be found in the Clinical Guidelines for the Management of Substance Use During Pregnancy, Birth and the Postnatal Period.[31]

[31] www.health.nsw.gov.au/aod/professionals/Pages/substance-use-during-pregnancy-guidelines.aspx

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Appendices

A. Drug–drug interactions (DDIs)

Drug class	Drug(s) within class	Clinical effect and suggested management
Alcohol	Alcoholic drinks Medications containing alcohol	Alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of buprenorphine (BPN). Use with caution.
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.
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz Nevirapine Etravirine Delavirdine	Significant pharmacokinetic interactions between NNRTIs and sublingual (SL) BPN 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.

Drug class	Drug(s) within class	Clinical effect and suggested management
Antiretrovirals: Protease inhibitors (PIs)	Atazanavir Ritonavir	Treatment with atazanavir or atazanavir/ritonavir may result in elevated levels of BPN. If atazanavir +/- ritonavir is initiated once the patient is stable on long-acting injectable buprenorphine (LAIB), monitor for signs and symptoms of over-medication with BPN and consider (a) dose reduction of LAIB or (b) transfer and treatment with SL BPN.
Benzodiazepines and other central nervous system (CNS) depressants	Alcohol Non-benzodiazepine sedatives/hypnotics Anxiolytics Tranquilizers Muscle relaxants General anaesthetics Antipsychotics 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 BPN formulations. Patients should be advised of the extreme danger of concomitant use of sedatives while receiving LAIB treatment.
CYP3A4 inhibitors	Macrolide antibiotics, azole-antifungal agents, protease inhibitors e.g. Erythromycin Ketoconazole Ritonavir Nelfinavir Indinavir Intraconazole	An interaction study of BPN with ketoconazole resulted in increased Cmax (approximately 50%) and AUC (approximately 70%) of BPN and, to a lesser extent, of the metabolite, nor-BPN. Patients receiving BPN should be closely monitored for signs and symptoms of BPN toxicity and may require dose reduction if combined with potent CYP3A4 inhibitors. The dose of either BPN or the CYP3A4 inhibitor may need to be adjusted accordingly. In practice, doses rarely need to be adjusted. Monitor for BPN withdrawal if the concomitant medication is discontinued after the patient is stable on LAIB.
CYP3A4 inducers	Rifampin Carbamazepine Phenytoin Phenobarbital	Concomitant use of CYP3A4 inducers with BPN may decrease BPN plasma concentrations, potentially resulting in suboptimal treatment of opioid dependence. It is recommended that patients receiving BPN should be closely monitored if inducers are co-administered. The dose of either BPN or the CYP3A4 inducer may need to be adjusted accordingly. In practice, doses rarely need to be adjusted. Monitor for signs and symptoms of BPN toxicity or overdose if the CYP3A4 inducer is discontinued after the patient is stable on LAIB.

Drug class	Drug(s) within class	Clinical effect and suggested management
Diuretics		BPN may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Drugs that affect the serotonin neurotransmitter system (also see separate entry for Monoamine oxidase inhibitors)	Selective serotonin reuptake inhibitors (SSRIs) Serotonin and norepinephrine reuptake inhibitors (SNRIs) Trazodone Tramadol Linezolid Intravenous methylene blue Tricyclic antidepressants (TCAs)	This combination may result in serotonin syndrome in high doses (e.g. overdose). Monitor for signs and symptoms of serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.
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.
Monoamine oxidase inhibitors (MAOIs)	E.g. Phenelzine Tranylcypromine Linezolid	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g. respiratory depression, coma). It is recommended that patients receiving BPN and MAOI are closely monitored. Exacerbation of the opioid effects may occur, based on experience with morphine.

Drug class	Drug(s) within class	Clinical effect and suggested management
Opioid analgesics	Opioids	BPN may reduce the effects of opioid analgesics through receptor blockade. Patients requiring analgesia should include non-opioid approaches (e.g. non-steroidal anti-inflammatory drugs [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 patients receiving BPN. The potential for overdose also exists with a full agonist, especially when attempting to overcome BPN partial agonist effects, or when BPN plasma levels are declining.
Opioid antagonists	Naltrexone Naloxone Nalmefene	Opioid antagonists should generally not be used outside of emergency situations in patients in opioid agonist treatment, including LAIB. Naloxone may be administered in response to an opioid overdose; multiple injections or an infusion of naloxone may be required. For patients with opioid dependence currently receiving BPN treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of BPN administration may be blocked by naltrexone.

B. Product information and contact details

Buvidal Weekly	Product Information (Australia)[32]
Buvidal Monthly	Product Information (Australia)[33]

Buvidal is manufactured by

Camurus Pty Ltd
Hyde Park Hub
223–225 Liverpool Street
Darlinghurst
NSW 2010
Australia

For medical enquiries:
Email: ausmedinfo@camurus.com
Phone: 1800 142 038

For general enquiries:
Email: australia@camurus.com

Sublocade	Product Information (Australia)[34]

Sublocade is manufactured by

Indivior Pty Ltd
78 Waterloo Road
Macquarie Park
NSW 2113
Australia

Email: sublocadeorders@indivior.com

Phone: 02 9025 0200

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

[33] www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02611-1

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

C. Microdosing and bridging transfers

The document over the page 'Interim Clinical Guidance: Outpatient Transfer from Methadone to Buprenorphine Using the Micro-dosing or Bridging Methods' was issued by NSW Health in 2023.

Prior to transfer, prescribers must obtain a temporary approval from the Ministry of Health. Apply via SafeScript NSW or manual form. Ensure sections **D Drug and Dose Information** and **E Other Treatment & Transfer Protocols** are completed. See the NSW Health website[35] for further application details and a link to the manual form.

[35] www.health.nsw.gov.au/pharmaceutical/doctors/Pages/application-forms.aspx

Interim Clinical Guidance:

Outpatient Transfer from Methadone to Buprenorphine Using the Micro-dosing or Bridging Methods

Introduction

Clients on the NSW Opioid Treatment Program (OTP) may be transferred from methadone to buprenorphine. There are three ways for accredited health professionals to enable this transfer:

- **Direct transfer** - standard approach for transfer from methadone to buprenorphine endorsed in current *NSW Clinical Guidelines – Treatment of Opioid Dependence* (page 26). Clients transferring from methadone doses ≤30mg can transfer directly to Buvidal® without micro-dosing or bridging medication.
- **Micro-dosing** (a modified 'Bernese' method) – may be considered for clients on higher doses of methadone (>40mg). Seek specialist advice if considering transfers for clients on methadone doses higher than 150mg.
- **Bridging** with a short-acting opioid – may be considered for clients on higher doses of methadone (>40mg). Seek specialist advice if considering transfers for clients on methadone doses higher than 150mg.

When using the direct transfer method, prescribers should refer to the *NSW Clinical Guidelines – Treatment of Opioid Dependence*.

The evidence base for micro-dosing and bridging methods is still developing. Use of opioid agonist treatment (OAT) medications in this context is considered 'off-label' and must be undertaken:

- in accordance with local clinical governance procedures
- in accordance with legislation, policies or procedures that govern off-label prescribing.

Prescribers are expected to use their professional judgement to determine the most clinically appropriate transfer method on a case-by-case basis. As the evidence continues to develop, this document will be updated in line with updates to clinical evidence and practice. Please refer to Appendix 1 for the version history of this document.

Note to readers: This document is based on the prescribing procedures developed by the Alcohol and Drug Service St Vincent's Health Network Sydney and Drug and Alcohol Services, South-Eastern Sydney Local Health District.

Purpose of this document:

To provide general guidance to prescribers intending to transfer clients from higher doses of methadone (>40mg) to buprenorphine use the micro-dosing or bridging methods on an outpatient basis. Services should design their local procedures in line with this guidance.

Relevant setting:

Outpatient

Definitions:

Table 1:

Clinical Opioid Withdrawal Scale (COWS)	An eleven-item, validated measure of the severity of a client's opioid withdrawal symptoms.
Opioid Agonist Therapy (OAT)	Long-term treatment with opioid medication (usually methadone or buprenorphine) as part of the treatment of opioid use disorder.
Short Opiate Withdrawal Scale (SOWS)	A 10-item self-report scale that provides a reliable and valid means of measuring the signs and symptoms of withdrawal among clients with opioid dependence.
Withdrawal Management	The management of withdrawal from a substance in a person who is dependent on that substance. Previously known as 'detox' or 'detoxification'.
Withdrawal Syndrome	A specific group of signs and symptoms that occur when a person who has developed tolerance to a particular drug (after regular use at high doses) stops or reduces use of the drug.

Planning:

The clinical situations in which clients are considered for methadone to buprenorphine transfer may vary significantly. For example, some stable clients will present electively requesting transfer. Other clients may have clinical features (for example, long QT interval demonstrated on ECG while on methadone) which make a more urgent inpatient transfer necessary.

Wherever possible, methadone to buprenorphine transfers should be planned well ahead of time, and when other matters (physical, psychological and social) are relatively stable, to improve the likelihood of success and decrease the likelihood of adverse outcomes.

Clinicians should inform clients about buprenorphine opioid agonist treatment, how the medication (duration of action, common effects and side effects) and treatment requirements (e.g. frequency of attendance for dosing, costs) differ to methadone. Clinicians should inform clients of the different methods for transfer from methadone to buprenorphine, the risks involved (see below) and what will happen if the transfer or stabilisation is unsuccessful. The involvement of peer workers may be of benefit to assist in this process.

Clinical risk regarding transfer processes:

Transfer from methadone to buprenorphine may be associated with complications including:

- precipitating withdrawal on initiating buprenorphine
- destabilisation of the client during transfer (including opioid or other substance use, or their medical, psychiatric or social condition)
- side effects from buprenorphine
- inability to transfer and stabilise on buprenorphine.

The risk of precipitating withdrawal is greater when transferring from long-acting opioids such as methadone. Further information on principles of safe transfer from methadone to buprenorphine are set out in the *NSW Clinical Guidelines – Treatment of Opioid Dependence*.

Assessment:

Unless otherwise known, the following information should be collected as part of an initial assessment.

- Methadone dose, dosing point, and prescriber
- Reason for requesting transfer from methadone to buprenorphine
- Past history of attempted transfers and outcome
- Past physical and psychiatric medical history
- Current medications and allergies
- Any concurrent substance use:
  - Substances being used
  - Quantity, frequency and duration of use
  - Route of administration
  - Previous withdrawal experiences, including a predicted severity of withdrawal based on recent patterns of use and past withdrawal experiences

Authority to prescribe and supply OAT:

The *Poisons and Therapeutic Goods Act 1966* (NSW) prohibits the prescribing and supply of a drug of addiction (Schedule 8 medicine) to a drug dependent person. However, a medical practitioner or nurse practitioner may apply to be authorised to prescribe or supply a drug of addiction to a drug dependent person for the purpose of opioid dependence treatment under the OTP. This authority is issued by the Pharmaceutical Regulatory Unit of the NSW Ministry of Health.

New application forms related to the management of patients under the NSW OTP may be found on the NSW Health website. These forms have been reviewed and updated to streamline the application process, improve the health practitioner experience and to align with the online process for applying for authorities which will be available to health practitioners later this year. Additionally, these forms support new treatment and transfer protocols including micro-dosing and bridging transfers and other OAT.

The new application forms replace the old OTP application forms that were on the NSW Health website and in the OTP Clinical Guidelines.

Please note that there are declarations at the beginning (except for the exit form) and end of the forms. Applicants must ensure they complete and submit both declarations.

Interim Micro-dosing Guidance

Micro-dosing involves a client continuing to take methadone while commencing small doses of sublingual buprenorphine. Buprenorphine is up titrated while methadone is down titrated over approximately one week.

Client identification and risk assessment for micro-dosing

- Most clients looking to electively transfer from methadone to buprenorphine are suitable to transfer via micro-dosing in an outpatient setting. Inpatient transfers should be undertaken in the following circumstances:
  - Doses >150mg – at this time there are no reported cases of ambulatory micro-dose transfers from methadone to buprenorphine at doses >150mg.
  - Cirrhosis – due to the potentially altered pharmacokinetics of methadone and buprenorphine metabolism for people with cirrhosis, inpatient transfer is recommended.
  - Inconsistent dosing/lifestyle pattern – micro-dosing requires either daily attendance for transfer, or unsupervised management of a variable buprenorphine regimen. For those who miss regular doses or would not be suitable for unsupervised dosing, this may not be a suitable option.
- Occasionally clients will be referred for transfer due to medical reasons (e.g. long QT syndrome, drug-drug interaction).
- Unsupervised dosing can be trialled for clients who have been assessed as able to manage the daily changes in buprenorphine dosing, but this will require careful planning, scripting and discussion with pharmacy to simplify dosing as much as possible. The following criteria should be considered on a case-by-case basis:
  - Already prescribed unsupervised methadone dosing
  - No concomitant unsanctioned substance use
  - Stable accommodation.

Micro-dosing method to transfer a client from methadone to sublingual buprenorphine

- Apply for authority using Application for Authority to Prescribe or Supply Methadone, Buprenorphine, or other Opioid Agonist Therapy (OAT) Treatment under the NSW Opioid Treatment Program (OTP). Ensure Section D *Drug and Dose Information* and Section E *Other Treatment & Transfer Protocols* are completed.
- Once approved, the authority will be granted for buprenorphine on an ongoing basis. Additionally, it grants the applicant authority to prescribe methadone for a specified time allowing for transfer treatment to occur. If they held the methadone authority for the patient prior to the transfer, the applicant is not required to submit an exit form for methadone.
- Administer COWS and SOWS each day; SOWS is based on symptoms reported in the previous 24 hours.

Table 2:

Day	Methadone dose	Buprenorphine dose	Throughout
0	X mg	0 mg	COWS Symptomatic relief* Support + encouragement
1	X mg	0.2 mg BD or 0.4 mg mane	
2	X mg	0.4 mg BD	
3	X mg	2 mg	
4	X mg	4 mg	
5	X mg	8 mg	
6	½X mg	16 mg	
7	¼X mg	16-32 mg Clients may commence depot buprenorphine weekly at this point (optional). See *Brief Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence*	

X = client's current methadone dose

*For example:

- Clonidine 50mcg up to QID PRN - clients should take while seated, and avoid if dizzy/light-headed
- Ondansetron 8mg up to BD PRN

Management of missed doses

Table 3:

	Recommended action
One day of missed methadone and buprenorphine	Recommence regimen at the most recent dosing schedule
Two-three days of missed methadone and buprenorphine	Complete COWS • If >24 – initiate onto buprenorphine • If <24 – recommence regimen at the most recent dosing schedule
Four - five days of missed methadone and buprenorphine	Complete COWS • If >13 – initiate onto buprenorphine • If <13 – commence procedure at day 6
More than 5 days of missed methadone and buprenorphine	Initiate onto buprenorphine
Note: Regardless of the number of days missed, prescribers are to discuss with clients their medication preference as they may prefer to return to methadone rather than continue with buprenorphine.	

Interim Bridging Guidance

This procedure involves stopping methadone and allowing several days of 'wash out' before commencing buprenorphine. A short acting opioid (e.g. oxycodone) is administered in the intervening period from last methadone dose to first buprenorphine dose to prevent the onset of severe withdrawal on stopping methadone.

Client identification and risk assessment for bridging using oxycodone

As the bridging method involves providing some unsupervised doses of a drug of dependence (oxycodone) to a drug dependent person, it is important to consider the suitability of the client to complete the transfer in an outpatient setting. Part of that assessment involves a detailed risk assessment around concomitant substance use, physical and mental health comorbidities, and social situation.

The criteria to be used to identify suitable clients are:

- Methadone doses 40-150mg daily. Clients transferring from high methadone doses (80-150mg) may benefit from an inpatient admission to undertake the transfer, as they are at greater risk of precipitated withdrawal, and often have more physical and mental health comorbidities that can complicate management.
- Methadone dose >150mg daily, should attempt to reduce their dose to 150mg. If this is not possible, then seek specialist advice and consider inpatient admission to undertake the transfer.
- Has previously been prescribed buprenorphine without severe adverse events.
- No history of allergy or anaphylaxis to buprenorphine or any other component of Buvidal®.
- Risk assessment (particularly important for assessing suitability for outpatient transfer setting)
    - Minimal unsanctioned opioid use (<1 day per week)
    - No illicit intravenous use of pharmaceutical opioids in the last month
    - No excessive use of other sedating substances: alcohol (excessive use defined as >4 standard drinks per day more than once a week), benzodiazepines (excessive use defined as >10mg diazepam equivalent daily)
    - Stable social situation: not at risk of coercion, no domestic violence, not experiencing homelessness, consider childcare arrangements if applicable.

Bridging method using oxycodone to transfer a client to Buvidal® (a form of Long-Acting Depot Buprenorphine)[1]

Oral oxycodone can be used as a 'bridge' between last methadone dose and initiation of Buvidal® to alleviate opioid withdrawal symptoms which are likely to follow cessation of methadone. The rationale for using oxycodone (rather than morphine) is:

[1] Advice in this document is directed at Buvidal® transfers specifically, as undertaking this process with Sublocade® is not advised. For information on transferring from Buvidal® to Sublocade®, see p 32 in the *Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence*.

- Modified release oxycodone (OxyContin®) is a tamper-resistant product (very difficult to inject), making it safer to supply as take-home medication
- any additional heroin use can be differentiated from oxycodone use in urine drug screens.

A conversion rate of oxycodone to methadone of 3-4:1 should be used, supplied in two divided doses per day (BD) using the Modified Release OxyContin® formulation. On the first day without methadone, the conversion rate will usually be 3:1. On the second day without methadone, the dose may be titrated up to 4:1 (administered in 2 divided doses) if required. On the day in which Buvidal® Weekly injection is commenced, a dose of immediate release oxycodone (Endone®) (one third of total dose administered on previous day) is administered immediately before the Buvidal® dose. The rationale is that Buvidal® takes 3 to 6 hours after the injection to start to have effect, and 12-24 hours to have full effect; a dose of immediate release oxycodone prevents onset of opiate withdrawal until onset of Buvidal® effect. Oxycodone dosing is summarised below.

Note: Clinicians should explain to clients that dispensed medications for use at home will not be replaced in the event of any mishap (e.g. through loss or theft).

Table 4:

Day	Oxycodone formulation and dose calculation
1	Oxycodone MR (OxyContin®) 3:1 conversion e.g. for 50mg methadone, give total daily dose of 150mg OxyContin® as divided dose i.e. 75mg OxyContin® BD
2	Oxycodone MR (OxyContin®) 3-4:1 conversion (depending on clinical presentation, COWS/SOWS/local drug and alcohol review form) E.g. for 50mg methadone, give total daily dose of between 150mg-200mg OxyContin® as divided dose i.e. between 75mg-100mg OxyContin® BD
3	Oxycodone immediate release (Endone®) 4:1 conversion and give one-third of that dose as a single supervised dose immediately prior to Buvidal® administration E.g. for 50mg methadone, give 200mg/3 = ~65mg oxycodone immediate release

Buvidal® dosing

For clients transferring from >40mg methadone, an initial Buvidal® Weekly dose of 24mg is recommended. For clients transferring from <40mg, administer Buvidal® Weekly 16mg dose. The clients should be reviewed daily on subsequent days to monitor for withdrawal symptoms. If required, additional Buvidal® Weekly 8mg doses can be administered (up to 24 hours apart, and to a maximum of 32mg total dose in the first week).

Subsequent Buvidal® doses (Weekly or Monthly, as selected by patient and prescriber) can be administered 5 days after the first Buvidal® Weekly dose.

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Reviewing clients during transfer procedure

Clients undertaking outpatient transfers should attend each morning on days 1-3 during the transfer process. Morning reviews will take place in person, and afternoon reviews will generally be scheduled via telehealth for between 2-4pm. The client's address, contact number, and emergency contact details should be confirmed on the first day of the transfer. This is outlined in Table 5 below.

Table 5:

Day	Clinical procedures	Medication	Admin tasks
(At least one week prior to transfer)	Client review to discuss transfer procedures and ensure all necessary arrangements in place	• Continue usual methadone dosing • Day prior: continue usual methadone dosing or reduce methadone dose by up to 50%	Submit PRU application *Application for Authority to Prescribe or Supply Methadone, Buprenorphine, or other Opioid Agonist Therapy (OAT) Treatment under the NSW Opioid Treatment Program (OTP).* Ensure Sections D and E are completed.
1	**Morning review** (in-person): Check with client s/he ceased methadone dose previous day and has had nil dose today • Use local Drug & Alcohol Review Form • COWS and SOWS* • Discuss with addiction medicine specialist or on-call AOD medical officer if concerned e.g. intoxication. **Afternoon review** (structured telehealth): • Use local Drug & Alcohol Review Form • SOWS* • Discuss with addiction medicine specialist or on-call AOD medical	• Oxycodone MR (OxyContin®)** ○ First dose supervised administration ○ Second dose given as individually packaged takeaway ○ Dose conversion: usually 3:1 • Consider need for other medications e.g. antiemetics, simple analgesia, buscopan. **NB provision of benzodiazepines is not recommended.** • Provide overdose response with take home naloxone and overdose brief intervention	• Confirm methadone last dose details with dosing point and confirm methadone script inactivated. • Provide SOWS form to client, instruct to complete in the afternoon before next oxycodone

Day	Clinical procedures	Medication	Admin tasks
	officer if concerned e.g. intoxication.		
2	**Morning review** (in-person): • Use local Drug & Alcohol Review Form • COWS and SOWS* • Discuss with addiction medicine specialist or on-call AOD medical officer if concerned e.g. intoxication. **Afternoon review** (structured telehealth): • Use local Drug & Alcohol Review Form • SOWS* • Discuss with addiction medicine specialist or on-call AOD medical officer if concerned e.g. about intoxication.	• Oxycodone MR (OxyContin®)** ○ First dose supervised administration ○ Second dose given as individually packaged takeaway dose ○ Dose conversion: up to 4:1 • Consider need for symptomatic medications as for Day 1.	• Review self-completed SOWS from previous day and file in medical record • Provide SOWS form to client, instruct to complete in the afternoon before next oxycodone.
3	**Morning review** (in-person): • Use local Drug & Alcohol Review Form • COWS and SOWS* • Discuss with addiction medicine specialist or on-call AOD medical officer if concerned e.g. intoxication. **Afternoon review** (structured telehealth): • Use local Drug & Alcohol Review Form • SOWS* • Discuss with addiction medicine specialist or on-call AOD medical	• Oxycodone IR** ○ Give single supervised dose immediately prior to Buvidal® administration ○ Usually administer 1/3rd of total day 2 dose • Buvidal® Weekly subcut injection.	• Review self-completed SOWS from previous day and file in medical record. • Provide SOWS form to client, instruct to complete in the evening.

Day	Clinical procedures	Medication	Admin tasks
	officer if concerned e.g. intoxication.		
4	**Morning review** (structured telehealth): • SOWS* • Discuss with addiction medicine specialist or on-call AOD medical officer if concerned e.g. about intoxication. *(Clients should be given the option of an in-person review if preferred.)*	• Advise client about the option of a top-up Buvidal® injection over next few days if required. • Organise next scheduled Buvidal® dose 7 days after first dose.	• Review self-completed SOWS from previous day and file in medical record

***SOWS:** Clients should complete 2 SOWS forms per day. The first is completed on-site prior to the first dose of oxycodone, and the second should be completed at home before taking the second dose of oxycodone. Clients should be asked to return the forms to the clinic the following day. Forms can be located at: https://www.asam.org/docs/default-source/education-docs/sows_8-28-2017.pdf

****Dose calculation oxycodone:** see Table 4 for suggested dose conversions and administration considerations.

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