

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

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Introduction

This Brief guideline is to be used in conjunction with the full version of the Clinical guidelines for the use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence; and with the NSW Clinical Guidelines: Treatment of Opioid Dependence 2018 and the National Guidelines for Medication-Assisted Treatment of Opioid Dependence 2014.

Acronyms

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

Depot buprenorphine products: Buvidal[®] and Sublocade[®]

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

Buvidal[®] is a modified release formulation of BPN, registered in Australia for 'maintenance treatment of opioid dependence within a framework of medical, social and psychological support'. Buvidal[®] is designed to be administered by subcutaneous injection once a week (Buvidal[®] Weekly) or once a month (Buvidal[®] Monthly).

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

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

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

Framework for treatment with depot BPN products

The key elements of safe and effective BPN treatment for opioid dependence are (a) safe and effective use of medicine; (b) regular clinical reviews and monitoring; (c) participation in psychosocial interventions; and (d) addressing medical, mental health and social comorbidities.

It is essential that patients are provided accurate information and options regarding their medication and treatment, as part of informed decision making and consent. Once-a-week and once-a-month depot injections reduce the need for daily supervised and/or 'take-away' doses of Sublingual (SL) BPN formulations. Potential benefits of depot BPN treatment include:

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

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

Buvidal[®] and Sublocade[®] must be administered by registered health practitioners. Buvidal[®] and Sublocade[®] medications must not be handled by, or dispensed to patients or carers.

Delivering treatment with depot BPN

The key characteristics of Buvidal[®] and Sublocade[®] and recommended dosing regimens are summarised in Table 2. Specific recommendations regarding medication regimens for each product are described below. See the full guidelines and product information for an overview of the clinical pharmacology, evidence of safety and efficacy of these products, and issues regarding special populations. There is no evidence directly comparing the safety or efficacy of Buvidal[®] and Sublocade[®] products.

Dosing recommendation for Buvidal®

Transferring from SL BPN. Patient should usually be treated with ≥ 7 days of SL BPN prior to transferring to Buvidal®, with either Buvidal® Weekly or Buvidal® Monthly starting on the day after the last daily SL dose. Buvidal® doses are 'matched' to SL BPN doses as shown in Table 1.

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

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

Patients should be reviewed prior to the next scheduled dose and assess for adverse events, withdrawal, cravings, substance use and patient's rating of dose adequacy. Titrate doses upwards or downwards accordingly. Steady-state equilibrium is usually achieved after three to four doses.

Commencing BPN treatment with Buvidal®.

Whilst not recommended as routine practice, Buvidal® Weekly can be initiated directly from short acting opioids (e.g. heroin) or after less than 7 days of SL BPN treatment (e.g. a patient unable to access dosing sites for daily SL dosing).

For patients reporting current dependent opioid use, initiate Buvidal® Weekly 24mg doses and review for subsequent dose titration.

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

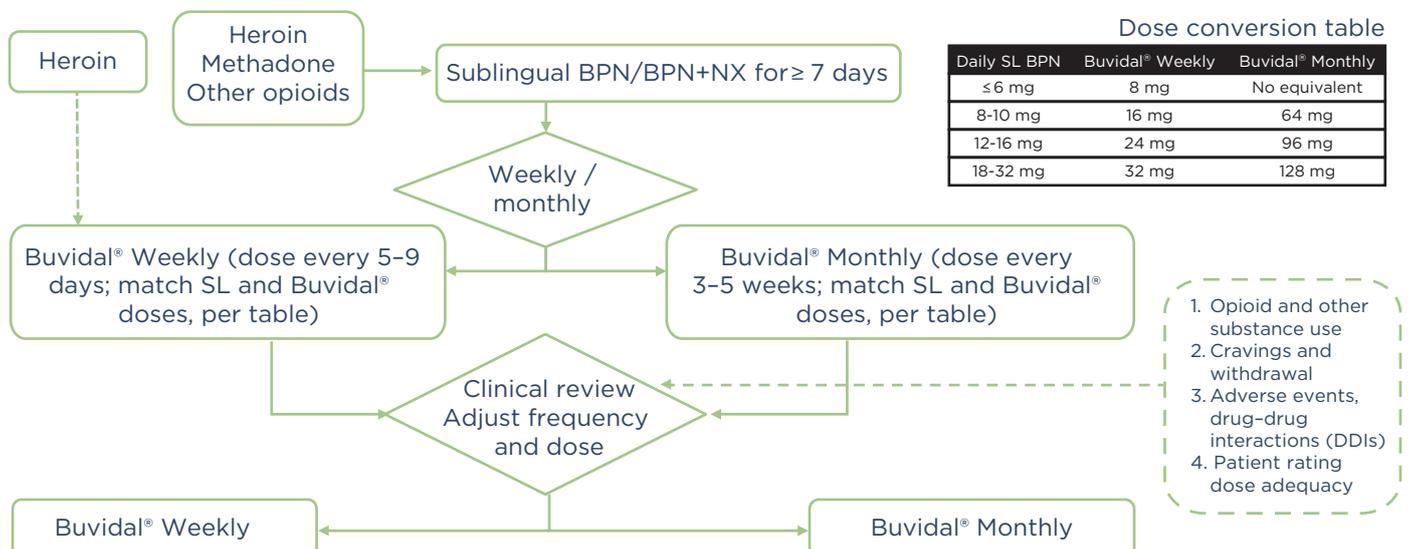
- Buvidal® Weekly doses may be given up to 2 days before or after the weekly time point (days 5-9),
- Buvidal® Monthly may be given up to 1 week before or after the monthly time point (weeks 3-5).

If a dose is missed, the next dose should be administered as soon as possible. Re-induction may be required if >14 days has elapsed between Buvidal® Weekly doses, or >8 weeks between Monthly doses.

Supplemental or 'top up' BPN doses.

Supplemental Buvidal® injections may be used if clinically indicated (patient experiencing opioid withdrawal, cravings or persistent unsanctioned opioid use). Patients may receive additional 8 mg Buvidal® Weekly injections at least 24 hours apart, to a maximum total weekly dose of 32 mg, and maximum total monthly dose of 160mg. If supplemental Buvidal® Weekly doses cannot be administered, supplemental doses of SL BPN (≤ 8 mg daily) may be used for a limited period of time until the next depot injection can be organised.

Figure 1: Overview dosing with Buvidal®



Dosing recommendations with Sublocade®

Commencing Sublocade® treatment. Sublocade® treatment requires preceding treatment with SL BPN for at least 7 days, preferably achieving SL doses ≥ 8 mg daily. Sublocade® is generally not recommended for patients on daily SL BPN doses < 8 mg.

The first Sublocade® dose should usually be administered approximately 24 hours after the last SL BPN dose but may be administered on the same day. For most patients, commence 300mg doses for the first 2 months (2 x monthly doses), reflecting 'loading' doses that elevate plasma BPN levels more rapidly during the initial treatment period. Sublocade® may be initiated with 100mg doses where there may be safety concerns of high BPN plasma levels (e.g. severe hepatic disease, DDIs).

After the initial two monthly Sublocade® doses, select between 100mg or 300mg 4-weekly doses. For most patients, 100mg 4-weekly Sublocade® doses will be adequate, maintaining plasma levels (at steady state equilibrium) achieved with the first two 300mg 'loading' doses. Maintenance

300mg doses should be considered for those patients who had previously stabilised on high dose SL BPN (e.g. 24 to 32mg daily), or continue to experience cravings, withdrawal or unsanctioned opioid use during the first 2 month period of Sublocade® dosing or with 100mg Sublocade® doses.

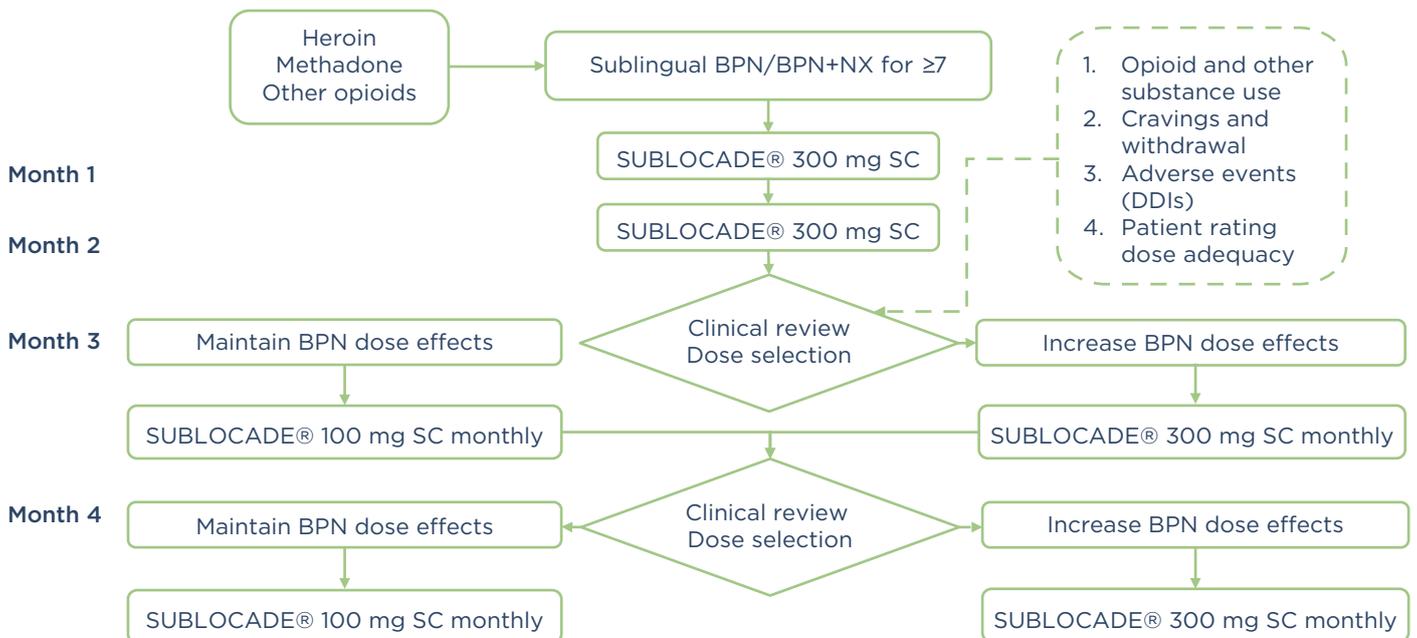
Sublocade® flexible dosing schedules. Sublocade® doses can be administered up to 2 days ahead of a scheduled dose (i.e. 26 days since the last injection), or up to 14 days after the 28 day interval (i.e. to 42 days since the last injection) without dose adjustments.

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

Supplemental or 'top up' BPN doses.

Supplemental SL BPN doses may be given if clinically indicated (patient experiencing opioid withdrawal, cravings or persistent unsanctioned opioid use). Additional SL BPN (≤ 8 mg daily) may be used for a limited period of time until the next depot injection can be organised.

Figure 2: Overview dosing with Sublocade



Safety issues regarding use of depot products

Precautions and contraindications. Depot products should not be administered to anyone hypersensitive to BPN or any of the excipients of Buvidal® or Sublocade® (see Product Information for details). Precautions regarding the use of Buvidal® and Sublocade® are similar to treatment with SL BPN and include patients with high-risk sedative use (e.g. alcohol, benzodiazepines), severe hepatic disease, cardiac arrhythmias, and respiratory depression. (see Product Information for details).

Adverse events (AEs). Both depot products can be associated with local injection site AEs – redness, pain, tenderness and swelling in 5-10% patients. These are usually mild, transient and resolve spontaneously. Sublocade® doses appear to be more commonly associated with a palpable lump at the injection site, which dissolves with time. Systemic AEs as per SL BPN (e.g. nausea, headache, constipation).

Drug-drug Interactions (DDI). DDIs are expected to be the same as for SL BPN, however the long duration of depot BPN effects may result in prolonged DDI. If concerns, stabilise on SL BPN and monitor DDI before transferring to depot BPN products.

Pregnancy and breastfeeding. SL BPN has an acceptable safety profile and is effective in pregnancy. There is a lack of research data on the safety and effectiveness of depot BPN formulations in pregnancy and breastfeeding. A neonatal opioid withdrawal syndrome is likely to occur. Pregnant women on depot BPN should be transferred to SL BPN, although may be continued on depot products if the potential benefit justifies the potential risks to the mother and baby.

Driving, operating machinery. BPN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned about driving or operating hazardous machinery.

Withdrawal from depot BPN products. The prolonged duration of action of the depot products means that withdrawal symptoms are likely to emerge long after the last depot dose. Withdrawal features may emerge 4-12 weeks after last Buvidal® Monthly dose, or 1-4 weeks after last Buvidal® Weekly dose. Peak withdrawal features may emerge 4-24 weeks after last 300mg dose or 4-12 weeks after last 100mg dose. Withdrawal symptoms may persist for weeks (or months), and are expected to be less severe than withdrawal from shorter-acting opioids. Although there is little documented experience of withdrawal from depot BPN products. It is generally recommended to taper the depot dose to the lowest possible before discontinuing treatment, and to review the patient at regular intervals.

Administration of depot products by other routes. Both depot products are intended for subcutaneous administration and *should never be injected intramuscularly, intra-dermally, intravenously or intra-arterially*. For this reason, depot formulations must be administered by a suitable health care professional, and never be dispensed or supplied directly to the patient or carer.

Transfer from methadone: there is limited experience and no documented evidence regarding transferring patients from methadone directly to depot BPN products. Transfer to SL BPN is recommended for at least 7 days prior to commencing depot treatment.

Special populations, treatment settings and clinical scenarios. The use of depot BPN products in certain patient populations and treatment settings (correctional facilities, hospitals, residential rehabilitation), and in the management of particular clinical scenarios (acute and chronic pain management, overdose, intoxicated presentations) is described in the full Guidelines document.

Table 2: Overview of BPN products available for treatment of opioid dependence in Australia

	SL Suboxone® and Subutex®	Buvidal® Weekly and Monthly	Sublocade®
Formulations	<p>Suboxone® contains buprenorphine (BPN) and naloxone in 4:1 ratio 2/0.5mg and 8/2mg sublingual film</p> <p>Subutex® contains buprenorphine in 0.4mg, 2mg and 8mg sublingual tablets</p>	<p>Buvidal® Weekly and Monthly contain BPN in FluidCrystal® injection depot technology Subcutaneous (SC) injections in prefilled syringes with 23 gauge needle. Administration via upper arm, thigh, abdomen or buttocks</p> <p>Buvidal® Weekly: 8mg/0.16mL, 16mg/0.32mL, 24mg/0.48mL; 32mg/0.64mL</p> <p>Buvidal® Monthly: 64mg/0.18 mL, 96mg/0.27 mL; 128/0.36 mL</p>	<p>Sublocade® contains BPN in the ATRIGEL® Delivery System</p> <p>SC injections in prefilled syringes with 19 gauge needle administered in abdomen</p> <p>Monthly doses: 100mg/0.5mL or 300mg/1.5mL</p>
Storage requirements	Store at room temperature (below 30°C)	Store at room temperature (below 25°C) Do not refrigerate or freeze.	Cold storage requirements (2-8°C). May be stored at room temperature (below 25°C) for up to 7 days before use. Remove from cold storage for at least 15 minutes prior to SC injection
Clinical pharmacology	<p>Bioavailability 10-30%</p> <p>Onset effects within 1 hour, with peak effects 2-4 hours after dose</p> <p>Duration effects usually 24 hours but dose dependent and can vary from 8 to 72 hours</p>	<p>Bioavailability = 100%</p> <p>Time to peak plasma level (tmax)</p> <ul style="list-style-type: none"> • Buvidal® Weekly = 24hrs • Buvidal® Monthly = 6-10 hrs <p>Half life</p> <ul style="list-style-type: none"> • Buvidal® Weekly = 3-5 days • Buvidal® Monthly = 19-25 days <p>Steady-state equilibrium by 4th dose</p>	<p>Bioavailability = 100%</p> <p>Time to peak plasma levels (t_{max}) = 24hrs</p> <p>Half life = 43 to 60 days</p> <p>Steady-state equilibrium by 2nd (300/100mg) to 6th dose (300/300mg)</p>
Frequency of dosing	Daily, two or three day doses Take-aways and unsupervised dosing available for low risk	<p>Buvidal® Weekly dose can be administered every 7±2 days (5-9 day schedule)</p> <p>Buvidal® Monthly dose can be administered every 4±1 weeks (3-5 week schedule)</p>	Sublocade® dosed every 4 weeks (26-42 day schedule)
Key Drug - Drug Interactions (DDIs)	<p>Systemic BPN DDI include:</p> <ul style="list-style-type: none"> - Opioids agonists: can reduce effects other opioids (blockade); BPN may precipitate withdrawal on induction - Sedatives (e.g. benzodiazepines, alcohol, TCAs, antipsychotics, gabapentinoids): sedation, respiratory depression, overdose <p>A number of potential DDI can occur but are rarely of clinical significance (e.g. interactions with medications that induce or inhibit CYP450 and can lower or increase BPN plasma levels); or are rare (e.g. serotonergic syndrome in combination with medication such as SSRIs, MAOIs, tramadol; or medications that can cause QT prolongation and increase risk of cardiac arrhythmias).</p> <p>Long duration of effects of depot BPN products precludes timely dose adjustment for DDI. If concerned re: potential DDI - initiate treatment with 'short acting' SL BPN for 1-4 weeks, monitor DDI and adjust medications accordingly, prior to transfer to depot injection.</p>		

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

Regulatory requirements

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

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

Getting support and more information

National Guidelines for Medication-Assisted Treatment of Opioid Dependence (MATOD) [http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/AD14DA97D8EE00E8CA257CD1001E0E5D/\\$File/National_Guidelines_2014.pdf](http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf)

NSW Clinical Guidelines: Treatment of Opioid Dependence 2018 <https://www.health.nsw.gov.au/aod/Publications/nsw-clinical-guidelines-opioid.pdf>

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

Drug and Alcohol Specialist Advisory Service (DASAS) <https://www.svhs.org.au/our-services/list-of-services/alcohol-drug-service/drug-alcohol-specialist-advisory-service>

Alcohol & Drug Information Service (ADIS) <https://www.svhs.org.au/our-services/list-of-services/alcohol-drug-service/alcohol-drug-information-service>

Opioid Treatment Line (OTL) <https://www.svhs.org.au/our-services/list-of-services/alcohol-drug-service/the-opioid-treatment-line>

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

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

Sublocade® product information AUS

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



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