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

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the best available evidence at the time of development of this publication. This guideline includes recommendations by clinical experts where research evidence does not currently exist. Wherever guidance is provided that is not directly informed by research evidence, the document will highlight these sections as "Consensus Statement" (CS).

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Executive summary

This Clinical Guideline has been developed to inform decision-making by clinicians prescribing and/or patients being treated with Buvidal® long-acting injected buprenorphine preparations.

Buvidal® is a prolonged-release formulation of buprenorphine (BPN), registered in the UK for 'Treatment of opioid dependence within a framework of medical, social and psychological treatment'. Treatment is intended for use in adults and adolescents aged 16 years or over. Buvidal® is designed to be administered by subcutaneous injection once a week or once a month.

Weekly Buvidal® 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.
Monthly Buvidal® 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.

Framework for treatment with depot BPN products

Key elements of safe and effective opioid substitution treatment (OST) include; safe and effective use of medicine; regular clinical reviews and monitoring; participation in psychosocial interventions; and addressing medical, mental health and social comorbidities.

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

However, depot BPN formulations may not suit all patients, and some will prefer SL BPN or methadone treatment, and these options should be available. Buvidal® must be administered by registered health practitioners and must not be handled by or dispensed to patients or carers.

Dosing recommendation for Buvidal®

Patients treated with SL BPN formulations may be transitioned directly to Buvidal® prolonged-release injections starting on the day after the last daily SL treatment dose (see conversion recommendations in Table 1). Patients should be reviewed prior to the next scheduled dose and assessed for adverse events, withdrawal, cravings, substance use and the patient's rating of dose adequacy. Individual clinical titration of doses may be required on subsequent doses, recognising that the dose effects of depot formulations are likely to increase with BPN accumulation until steady state equilibrium is achieved (usually after 4 doses).

Table 1: Dose conversions between SL BPN, depot weekly Buvidal® and monthly Buvidal® doses [1 2 3 4 5]

Dose of daily sublingual buprenorphine	Dose of daily Espranor® ⁎	Dose of weekly Buvidal®	Dose of monthly Buvidal®
2-6mg	2-4 mg	8mg	
8-10mg	6-8mg	16mg	64mg
12-16mg	10-12mg	24mg	96mg
18-24mg	14-18mg	32mg	128mg

⁎ 25-30% higher bioavailability for Espranor® than for sublingual Subutex® tablet

Commencing BPN treatment with Buvidal®.

Depot BPN should be started when objective and clear signs of mild to moderate withdrawal are evident. For patients who have not previously been exposed to BPN a SL BPN test dose should be given prior to the administration of a weekly Buvidal® prolonged-release injection to confirm tolerability to BPN. A sublingual BPN 4 mg dose should be administered and the patient should be observed for an hour to confirm tolerability to BPN. The recommended starting dose of weekly Buvidal® for patients not previously receiving BPN is 16 mg, with one or two additional 8 mg doses at least 1 day apart. The recommended dose for the second treatment week is the total dose administered during the week of initiation.

A clinical decision may be made that a test dose is desirable to reduce the risk of precipitated withdrawal in patients who are not already receiving BPN. A validated tool such as the Clinical Opiate Withdrawal (COWS) scale can be used to support this assessment (e.g. COWS score of 10 or more). Clinicians should monitor levels of withdrawal so that the patient does not become too uncomfortable (CS).

Patients may be switched from weekly to monthly dosing or from monthly to weekly dosing based on the recommendations in Table 1. Patients can be switched from weekly to monthly Buvidal® after 4 weeks of treatment. In some instances, clinicians may consider switching sooner based upon an assessment of broader risks and overall treatment benefit (for example retention in treatment and/or patient wishes). Patients switching from weekly to monthly dosing will generally experience trough levels in the first few months similar to patients switching from SL BPN. Patients should be monitored for increased withdrawal or craving symptoms or other signs of instability. Titration to higher or lower doses may be required.

Flexible dosing

'Top-up' or supplemental doses of Buvidal® may be given if the patient experiences clinical features of opioid withdrawal, cravings or persistent unsanctioned opioid use. Examples include; during dose titration in the early stages of depot treatment; following drug-drug interaction (DDI); and delayed or interrupted depot dosing due to unforeseen circumstances such as travel, transport problems, or other commitments.

If clinically indicated, a maximum of one supplemental Buvidal® 8mg dose may be administered at an unscheduled visit between regular weekly and monthly doses. The maximum dose per week for patients who are on weekly Buvidal® treatment is 32mg with an additional 8mg dose (i.e. 40mg). The maximum dose per month for patients on monthly Buvidal® is 128 mg with an additional supplementary 8 mg dose (i.e. 136 mg). There may be circumstances where top up or supplemental doses of BPN are required but it is not possible to organise weekly Buvidal® 8mg doses (e.g. travel away from regular service providers). Supplemental low doses of SL BPN (e.g. 4mg or 8mg) may be used for a limited period until the next depot injection can be organised (CS).

Induction from other opioids: prescription opioids and methadone

To avoid precipitating symptoms of withdrawal, treatment with Buvidal® should be started when objective and clear signs of mild to moderate withdrawal are evident. Consideration should be given to the types of opioid used (that is long- or short-acting opioid), time since last opioid use and the degree of opioid dependence. For patients using heroin or short-acting opioids, the initial dose of Buvidal® must not be administered until at least 6 hours after the patient last used opioids. For patients receiving methadone, the methadone dose should be reduced to a maximum of 30 mg/day before starting treatment with Buvidal® which should not be administered until at least 24 hours after the patient last received a methadone dose. Buvidal® may trigger withdrawal symptoms in methadone-dependent patients.

Potential scenarios for discontinuing depot BPN treatment

Potential scenarios for discontinuing depot BPN treatment include: withdrawing off depot BPN (with goal of opioid abstinence), transfers to SL BPN, transfer to methadone / other OSTs, and transfer to oral naltrexone. Patients who have been in treatment for long enough to achieve steady state plasma levels of depot BPN are

likely to have a longer time course of reduction of BPN levels and therefore longer time course of withdrawal symptoms than those on depot BPN treatment for shorter periods. In general, the withdrawal syndrome from depot BPN is expected to occur several weeks to several months after the last dose, persist for longer, and may be of lower severity than withdrawal from SL BPN.

Wherever possible, patients should reduce depot BPN dose prior to discontinuing dosing. For patients on monthly Buvidal® this could involve switching to the weekly preparation before ceasing depot BPN. It is generally recommended to taper the depot dose to the lowest possible before discontinuing treatment. Patients and treatment plans should be reviewed regularly, with additional psychosocial support 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, however caution should be applied when considering extended use (beyond a few days) of sedatives or hypnotic medications. Given the risk of relapse patients who have withdrawn from depot BPN should be supplied with take-home naloxone.

Transfers to methadone

There is currently little clinical experience and no published studies regarding transfer from depot BPN to methadone. Given this lack of evidence, it is suggested that patients seeking to transfer from depot BPN to methadone should transition via SL BPN. Once stabilised on a dose of SL BPN for at least 4 weeks then transition to methadone can occur however it is recommended to initiate at low doses (20-30mg daily), reviewing regularly and titrating accordingly (CS).

Safety issues regarding use of depot products

Buvidal® should not be administered to anyone hypersensitive to BPN or any of the excipients [glycerol dioleate, phosphatidyl choline [soybean], and N-methyl-2- pyrrolidone (in weekly Buvidal®) and ethanol anhydrous (in monthly Buvidal®)]. Buvidal® should not be administered to patients with severe respiratory insufficiency, severe hepatic impairment or acute alcoholism or delirium tremens.

The features of hypersensitivity to BPN include rashes, hives, and pruritis. Most serious reported cases have involved bronchospasm, angioneurotic oedema, and anaphylactic shock. It should be noted that hypersensitivity to BPN is very rare.

Adverse events

Side effects of depot BPN are similar to the known safety profile of BPN administered sublingually with the exception of adverse events related to injection of the drug. The adverse reactions most frequently reported for BPN are headache, nausea, hyperhidrosis, insomnia, drug withdrawal syndrome and pain. Readers are referred to the Summary of Product Characteristics (SPC) for detailed information [1 2].

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

Pregnancy and breastfeeding

BPN remains an option for pregnant women who have already been initiated onto BPN but pregnant women should not be initiated onto BPN due to potential risks of opioid withdrawal in the foetus. BPN should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus. Pregnant women on depot BPN may be transferred to SL BPN. However, there may be clinical situations where pregnant women may not easily transfer to SL BPN.

Plasma levels of BPN seen with depot treatment are generally sustained over the weekly or monthly dosing interval compared to the concentrations with SL BPN which fluctuate based on the daily dosing interval. However it is not anticipated that this will result in significant differences in BPN levels in breastmilk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for depot BPN treatment and any potential adverse effects on the breastfed child from the drug or from the

underlying maternal condition. Breastfeeding for mothers on BPN is encouraged, even if the mother continues to use drugs, except where she uses cocaine or crack cocaine, or a very high dose of benzodiazepines [6]. Breast feeding may reduce the intensity and length of the Neonatal Abstinence Syndrome (NAS) and has been shown to improve outcomes.

Driving, operating machinery.

BPN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a vehicle or operating machinery. BPN plasma levels accumulate during the first four doses of Buvidal®. Patients should be cautioned about driving or operating hazardous machinery until the prescriber and patient are satisfied that depot BPN does not adversely affect their ability to engage in such activities.

Administration of depot products by other routes

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

Special populations, treatment settings and clinical scenario

The use of depot BPN products in certain patient populations and treatment settings (for example criminal justice, hospitals, and residential rehabilitation), and in the management of particular clinical scenarios (pain management, intoxicated presentations) is described in the full guidelines document.

Regulatory requirements

Buprenorphine is considered a controlled Class C drug under the 1971 Misuse of Drugs Act. It is subject to the Misuse of Drugs (Safe Custody) (Amended) Regulations 2007 detailing requirements for supply and possession in the UK. Buprenorphine sits in schedule 3 of the regulations. It is subject to special prescribing and safe custody requirements.

Prescriptions can be written on FP10, for dispensing to a healthcare professional to be administered in service or for administration by a suitably qualified community pharmacist where a Patient Specific Directive is in place. Buvidal® can be ordered by a service direct from a wholesale supplier where the service is in receipt of a Home Office license for the purchase of controlled drugs.

1 Background to guideline for depot BPN for the treatment of opioid dependence

This Clinical Guideline has been developed to inform decision-making by clinicians prescribing and/or patients being treated with Buvidal® long-acting injected buprenorphine preparations.

Buvidal® (developed under the name CAM2038 and manufactured by Camurus AB, and also known as Brixadi™ in the United States (US)) was approved in the UK in November 2018 for 'treatment of opioid dependence within a framework of medical, social and psychological support'. It is intended for use in adults and adolescents aged 16 years or over.

A National Institute for Health and Care Excellence (NICE) evidence summary in February 2019 found:

'Buprenorphine depot injection may be an option where there is a risk of diversion of opioid substitution medicines or concerns about the safety of medicines stored at home. It may also be an option for people who have difficulties adhering to daily supervised opioid substitution medication, such as for people who are working or in education. Buprenorphine depot injection may have a place in treating opioid dependence in people in custodial settings, where the risk of diversion and time needed for supervised consumption currently leads to challenges in supplying supervised medicines safely. However, the higher drug acquisition cost of buprenorphine depot injection compared with other treatments for opioid dependence will need to be taken into account.' [7]

This guideline has been developed for treatment using depot BPN in any clinical setting where patients receive OST including primary and secondary care, third sector services, private clinical settings and secure environments, and assumes that clinicians are familiar and experienced in the use of SL BPN products in the treatment of opioid dependence.

This guideline document has been informed by a synthesis of:

- published evidence for Buvidal® (CAM 2038)
- SPCs for Buvidal® [1] [2]
- NICE Opioid dependence: buprenorphine depot injection (Buvidal®) [7]
- The European Medicines Agency Assessment report for Buvidal® [8]
- expert consensus group meetings in February 2020.

This is the first clinical guideline for depot BPN treatment, beyond clinical trials, to be published in the UK. It is to be used in conjunction with Drug misuse and dependence: UK guidelines on clinical management [6] and the SPCs [1] [2]. The authors expect that future UK national guidelines will be revised to incorporate depot BPN preparations.

As clinical experience with depot BPN preparations is at an early stage, this guideline includes recommendations by clinical experts where research evidence does not currently exist. Wherever guidance is provided that is not directly informed by research evidence, the document will highlight these sections as "Consensus Statement" (CS).

It is anticipated that UK and international research will be published in the near future that may change guidance recommended in this document. The document will be reviewed in 12 months.

2 Introduction to OST with depot BPN

2.1 Overview of treatment model of care

OST (with methadone or BPN) has been demonstrated to be a safe and effective treatment approach for addressing opioid dependence and provides the opportunity to engage patients with other health and psychosocial interventions. Key elements of safe and effective OST include; safe and effective use of medicine; regular clinical reviews and monitoring; participation in psychosocial interventions; and addressing medical, mental health and social comorbidities.

The UK has hitherto been restricted to medications designed to be administered once a day (or up to alternate day dosing for a small proportion of patients treated with SL BPN). Risks associated with methadone and BPN (including diversion to others, injecting medications, and overdose risks) have resulted in a treatment model that is predicated on supervised dosing by an appropriate professional during the early stages of treatment, with take-home doses becoming available according to a risk assessment and risk mitigation strategies [6]. The reliance on daily dosing impacts greatly upon the cost and inconvenience of treatment for patients and service providers, and has been cited as a barrier to engagement and retention for some patients in treatment. The introduction of a depot BPN formulation into the UK treatment system represents a significant development in the model of care.

The availability of buprenorphine treatment with once-a-week and once-a-month depot injections is expected to be associated with several potential benefits:

- Greater convenience for patients as they will not have to attend dosing sites (pharmacies, clinics) on a frequent basis for supervised dosing or collection of medication. In the UK, many patients in SL BPN treatment attend daily or several times a week for supervised dosing or collection of medication. This can raise difficulties, in particular in rural settings where patients often have to travel large distances to reach dosing sites. This will also benefit patients for whom regular attendance at pharmacies is difficult (e.g. due to mobility problems, work issues, or caring responsibilities), or where regular attendance at a community pharmacy complicates confidentiality and can be associated with stigma and discrimination (e.g. in a rural town with only one pharmacy).

- Less risk of diversion and non–medical use of the medication, enhancing community safety. Despite a treatment system predicated on supervised dosing, a significant minority of patients engage in non–medical use of BPN (injecting, diversion to others, stockpiling)[9]. This is of particular concern in some settings for example criminal justice settings, and has limited the use of BPN in those environments in the UK, including formulations developed to reduce the risk of diversion, such as Espranor®.

- Potential for greater medication adherence and enhanced treatment outcomes for patients who struggle to attend regularly for dosing with SL BPN due to a range of issues including homelessness, cognitive impairment, domestic violence issues, child-care responsibilities, psychiatric co-morbidity, physical mobility problems (particularly with the UK's ageing treatment population), or regular episodes of incarceration. This group of patients is also often not suitable for large amounts of take-home doses of BPN, and can find themselves in a cycle of missed doses, polydrug use, and deteriorating health and social conditions. Some patients may benefit from less frequent (e.g. monthly) dosing requirements with the depot product, to maintain BPN adherence and to experience greater stability.

The introduction of BPN formulations is likely to have significant benefits for some patients and service providers. However, it may not suit all patients in OST, and some patients will prefer SL BPN or methadone

treatment, and these options should also be available. It is essential that patients are provided accurate information and options regarding their treatment as part of informed decision making and consent.

2.2 Evidence of efficacy of depot BPN in the treatment of opioid dependence

The efficacy and safety of Buvidal® in the treatment of opioid dependence have been established in clinical trials. Flexible doses of monthly Buvidal® formulations were shown to be 'non-inferior' to SL BPN in a double blind randomised control trial [10] on the primary endpoint of urine samples negative for illicit opioids (see appendix 1).

3 Clinical pharmacology

3.1 General

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

3.2 Formulations

Buvidal® is a depot formulation of BPN designed for administration by subcutaneous (SC) injection once a week or once a month.

The weekly Buvidal® formulation is available in four dose strengths containing 50mg/mL BPN as the active ingredient in prefilled syringes with a 23-gauge needle: 8mg (0.16mL), 16mg (0.32mL), 24mg (0.48mL) or 32mg (0.64mL).

The monthly Buvidal® formulation is available in three dose strengths containing 356mg/mL BPN as the active ingredient in prefilled syringes with a 23-gauge needle: 64mg (0.18mL), 96mg (0.27mL) or 128mg (0.36mL).

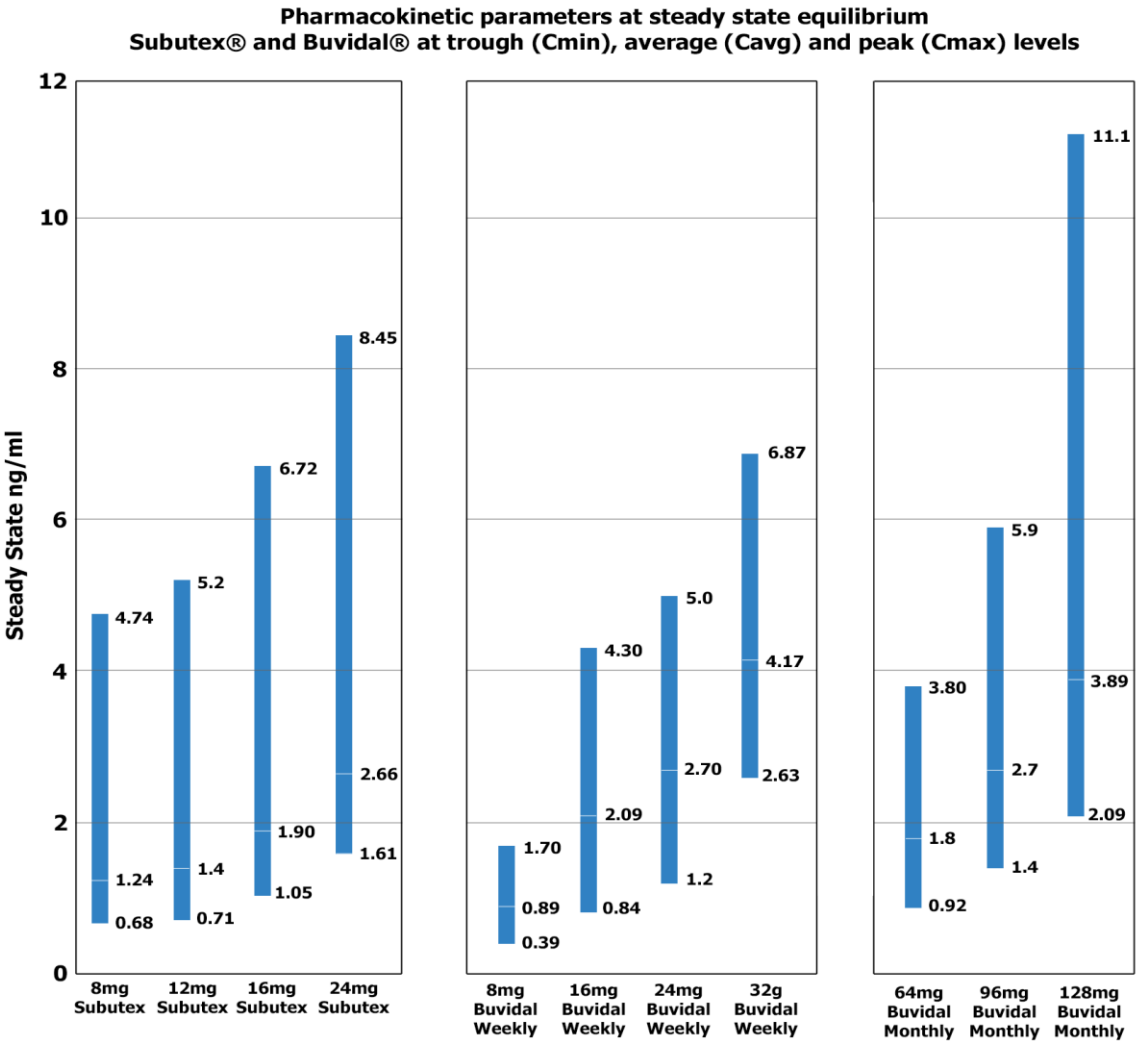
Buvidal® depots contain the active substance BPN in delivery system compositions based on the proprietary FluidCrystal® injection depot technology, a lipid-based liquid. When injected into the SC tissue the FluidCrystal® formulation absorbs interstitial aqueous body fluid and transforms from liquid to 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 over a week or a month depending on the composition. Excipients are described in the SPCs [1 2].

3.3 Overview of pharmacokinetic properties

The key pharmacokinetic properties of Buvidal® are detailed in the SPC [1 2].

It is important to recognise that repeated use of depot BPN formulations results in accumulation over time, and steady state equilibrium is achieved after four doses (weekly or monthly). The average (Cavg), peak (Cmax) and trough (Cmin) BPN plasma concentrations seen at steady state for SL and depot BPN formulations are shown in Figure 1 allowing a framework for comparing dose effects across different formulations.

Figure 1: Pharmacokinetic parameters – steady state



Whilst dose-proportional increases are seen within prolonged-release weekly or monthly formulations of BPN products, there is nevertheless considerable variation in BPN plasma levels between individuals, and Figure 1 should be interpreted as a guide only.

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 buprenorphine plasma levels as part of patient care. At this time, there is an inability to routinely or meaningfully measure BPN plasma levels or to assess opioid receptor occupancy in clinical practice. Clinicians should focus more upon individual patient responses to treatment with reviews of patient experience of withdrawal, cravings and continued substance use.

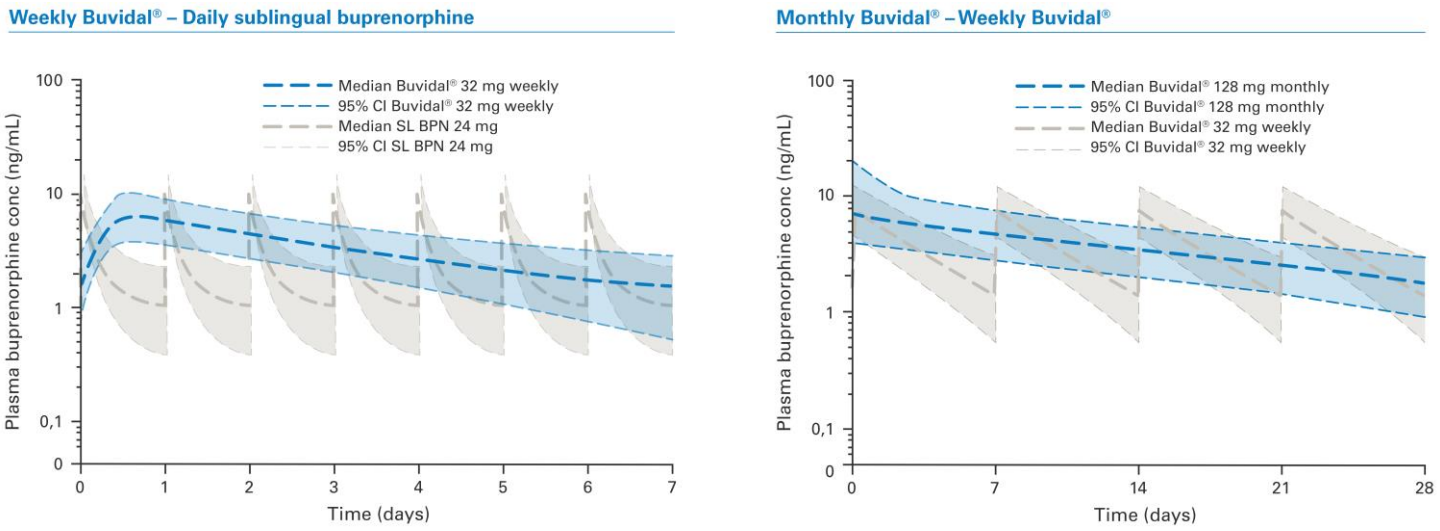
Whilst continued heroin or other opioid use may be a result of inadequate BPN dose it may also be related to social or other health issues. Plasma BPN levels only partially account for the clinical (pharmacodynamic) effects experienced by patients, such as prevention of opioid withdrawal and cravings, and blockade effects. A range of other factors impact upon the clinical effects of BPN and must be considered when titrating BPN doses to achieve desired clinical outcomes, including patient expectancy, concomitant medical (e.g. chronic pain, hepatic disease) and psychiatric 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 recommended and has very limited availability in the UK.

3.3.1 Absorption and onset of effects

After SC injection, BPN peak plasma concentrations (Cmax) are observed approximately 24 hours after the weekly Buvidal® injection and 6-10 hours after the monthly Buvidal® injection. After the initial BPN peak, the plasma BPN concentrations decrease slowly over the dosing interval.

Figure 2 illustrates the BPN plasma concentration-time profile for weekly Buvidal® injection (32mg) vs SL BPN (24mg/day) and monthly Buvidal® injection (128mg – labeled "CAM2038") vs weekly Buvidal® injection (32mg) [1]



3.3.2 Metabolism

The metabolism of BPN is largely the same irrespective of formulation. BPN is predominantly metabolised (N-dealkylation) by cytochrome P450 (CYP3A4) to the active metabolite norbuprenorphine, and both parent molecule and metabolite then undergo glucuronidation. Subcutaneous administration of depot BPN results in significantly lower plasma concentrations of norbuprenorphine metabolite compared to SL BPN, due to avoidance of first-pass metabolism invariably seen with some oral swallowing of sublingual doses.

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3.3.3 Elimination and duration of effects

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

- weekly Buvidal®: 3 to 5 days[1]
- monthly Buvidal®: 19 to 25 days [2].

With repeated dosing, BPN plasma levels accumulate until steady state equilibrium is achieved typically by the five half-lives of dosing, and needs to be considered when adjusting doses during the first few weeks or months of treatment. This typically means after the fourth dose (4 weeks for weekly Buvidal® and 4 months for monthly Buvidal®). The clinical effects of discontinuing BPN dosing will depend upon the formulation administered (e.g. weekly or monthly), the dose of depot administered (longer duration with higher doses), and the duration of

1 This is based on the half-life of Buvidal formulations and 90% elimination of the dose

treatment (whether steady state has been achieved following multiple doses).

Model simulations and clinical experience indicate that BPN plasma concentrations decrease slowly over time following the last injection and remain for extended periods – potentially up to 12 weeks for the monthly Buvidal® formulation and 3 weeks for the weekly formulation*****. The prolonged duration of effects of these 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 be protective against overdose following resumption of heroin or other opioid use.

3.3.4 Withdrawal, cravings, opioid blockade

Clinical trials indicate that Buvidal® is effective in reducing opioid withdrawal and cravings for opioid use. *Opioid blockade* is defined as the inhibition of the positive physiological and subjective effects (i.e. drug liking) of exogenous opioids, and is achieved through BPN by its greater affinity for mu opioid receptors than conventional opioids such as morphine, heroin, methadone, and oxycodone [10]. The blockade of subjective opioid effects has been demonstrated with clinical hydromorphone challenge studies with weekly Buvidal® products [12]. These studies are summarised in appendix 1.

3.4 Side effects and safety issues

3.4.1 Adverse events

Side effects of depot BPN are similar to the known safety profile of BPN administered sublingually [13] [14] with the exception of adverse events related to injection of the drug [10] .The adverse reactions most frequently reported for buprenorphine are headache, nausea, hyperhidrosis, insomnia, drug withdrawal syndrome and pain. Readers are referred to the SPCs for detailed information and appendix 2 [1] [2].

3.4.2 Contraindications

Buvidal® should not be administered to anyone hypersensitive to BPN or any of the excipients [glycerol dioleate phosphatidyl choline [soybean], and N-methyl-2- pyrrolidone (in weekly Buvidal®) and ethanol anhydrous (in monthly Buvidal®)]. Buvidal® should not be administered to patients with severe respiratory insufficiency, severe hepatic impairment or acute alcoholism or delirium tremens [1] [2].

The features of hypersensitivity to BPN include rashes, hives, and pruritis. Most serious reported cases have involved bronchospasm, angioneurotic oedema, and anaphylactic shock. It should be noted that hypersensitivity to buprenorphine is very rare.

3.5 Special Warnings

3.5.1 Risk of serious harm or death with intravenous administration

Care must be taken to avoid inadvertent injection of depot BPN into a blood vessel, intramuscularly 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 depot BPN forms a solid mass upon contact with body fluids which potentially could cause blood vessel injury, occlusion, or thromboembolic events.

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

BPN has been associated with life-threatening respiratory depression. Use depot BPN 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 depot BPN is discontinued as a result of compromised respiratory function, monitor patients for ongoing BPN effects for 3 weeks for weekly Buvidal® and, 3 months for monthly Buvidal®. The highest risk to patients will be when the medication is at peak dose (CS).

3.5.3 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 first dose of BPN is initiated before the effects of the full opioid agonist have subsided [1 2]. For patients receiving methadone, the methadone dose should be reduced to 30mg/day and administration of the test dose (if needed) should be at least 24 hours after the patient received a methadone dose.

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

Depot BPN provides higher than average sustained blood levels over a weekly or monthly period compared to the daily changes in BPN blood levels with SL BPN. Concomitant use of BPN with Central Nervous System (CNS) sedatives (e.g. alcohol, benzodiazepines, TCAs, gabapentinoids and antipsychotic medications), increases the risk of adverse reactions, including overdose, respiratory depression, and death. It remains unclear whether these risks are increased or reduced with depot BPN compared with SL BPN treatments.

Options to reduce this risk include stabilisation, reduction or cessation of benzodiazepines or other CNS depressants (usually through a monitored and gradual taper) 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.

Patient information regarding the risks of polysubstance use (including use of prescribed sedating medication), cautions regarding driving or operating machinery under such conditions, and the provision of take-home naloxone interventions are important risk mitigation approaches.

Note that additional headings under 'special warnings and precautions for use' in the UK summary of product characteristics (SPC) are: prolonged-release properties, dependence, precipitation of opioid withdrawal syndrome, renal impairment, acute pain management, use in children and adolescents, and class effects. For full details please see the SPCs [1 2].

3.5.5 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 B and, 2.8 times greater Child C)[15] 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 depot BPN has not been studied. Due to the long-acting nature of the product, adjustments to depot BPN dosages are not rapidly reflected in plasma BPN levels. Because BPN levels cannot be decreased rapidly, patients with moderate hepatic impairment should be

prescribed Buvidal® with caution. Buvidal® should not be used in patients with severe hepatic impairment.

An assessment of hepatic function (including liver function tests) and documentation of viral hepatitis status prior to treatment initiation with depot BPN is recommended [1 2]. Where a patient is identified as having clinically relevant liver disease (more than a mild elevation of LFTs) but not severe hepatic impairment, which is a contraindication to Buvidal® treatment, then an extended period of treatment with SL BPN (e.g. one-to-three months) may be an option (CS). This allows for monitoring of liver function to ensure that BPN does not worsen hepatic function, and for titration of BPN dose, prior to initiating depot BPN treatment. If Buvidal® is administered in preference to SL BPN for a patient with moderate hepatic impairment then a weekly formulation would be a pragmatic choice due to its quicker washout period as compared to the monthly prolonged-release formulation.

Monitoring of liver function may be considered for patients with mild to moderate liver disease and/or liver impairment after commencing treatment with depot BPN (e.g. clinical examination, liver function blood tests) and underlying causes, for example viral hepatitis, or alcohol use). Patients who develop moderate hepatic impairment while being treated with depot BPN should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of buprenorphine. Sedation following the initial dose may occur with high doses, and the patient should be warned accordingly. Termination of depot BPN treatment may be warranted if a patient's hepatic function significantly deteriorates; depot BPN should be stopped and specialist consultation is recommended. For patients who develop severe hepatic impairment, Buvidal® should be stopped and the patient switched to an alternative OST. As in moderate hepatic impairment the patient should continue to be monitored regularly following cessation of Buvidal®.

3.5.6 Use in patients at risk of arrhythmia

BPN has been observed to be associated with a prolonged QTc interval in some patients. Buvidal® SPCs recommend that caution should be exercised when co-administering Buvidal® with other medicinal products that prolong the QT interval and in patients with a history of long QT syndrome or other risk factors for QT prolongation. There are no cautions listed in the individual SPCs for oral BPN formulations.

In general, Buvidal® should be used with caution in patients with a history of long QT syndrome, or those taking Class IA antiarrhythmic medications (e.g. quinidine, procainamide, disopyramide), Class III antiarrhythmic medications (e.g. sotalol, amiodarone, dofetilide) or other medications that prolong the QT interval. Existing evidence suggests that QTc prolongation and risk of arrhythmias appears to be greater with methadone with a significant dose-dependent risk, and is 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 QT prolongation.

Key differences with depot BPN are that plasma levels of BPN may be consistently sustained as compared with SL BPN where levels will fluctuate. For patients at risk, more intensive workup prior to and or monitoring whilst on depot BPN treatment may be required. For assessment and management please refer to the Drug misuse and dependence: UK guidelines on clinical management [6].

If there are significant concerns regarding BPN effects on QT prolongation, consider initiating and maintaining treatment with SL BPN or weekly depot BPN treatment until further investigations have been completed, as it is simpler to discontinue BPN using SL daily or weekly depot formulations.

3.5.7 Other medical conditions

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

- respiratory insufficiency (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).
- CNS depression
- dependence
- hepatitis and hepatic events
- hepatic impairment
- renal impairment
- QT prolongation
- acute pain management
- opioids may cause orthostatic hypotension
- opioids may elevate cerebrospinal fluid pressure, which may cause seizures. Therefore, opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure
- opioids should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stenosis
- opioid-induced miosis, changes in the level of consciousness or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease
- opioids should be used with caution in patients with myxoedema, hypothyroidism, or adrenal cortical insufficiency (e.g. Addison's disease)
- opioids have been shown to increase intracholedochal pressure, and should be used with caution in patients with dysfunction of the biliary tract.

For details see the SPCs for Buvidal® [1] [2]. 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 medical conditions such as those listed above, it may be prudent to use sublingual BPN treatment or weekly Buvidal® until the impact of BPN has been assessed, enabling easier dose titration and avoiding prolonged plasma levels from monthly depot injections (that cannot be reversed).

3.5.8 Driving, operating machinery

BPN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a vehicle or operating machinery. BPN plasma levels accumulate during the first four doses of Buvidal®. Patients should be cautioned about driving or operating hazardous machinery until the prescriber and patient are satisfied that depot BPN does not adversely affect their ability to engage in such activities. People on a stable dose may not be at higher risk, providing the dose has been stabilised over some months and they are not using other impairing drugs. DVLA regulations on fitness to drive should also be considered, together with section A7 ‘Drugs and driving’ of Drug misuse and dependence: UK guidelines on clinical management [6].

3.5.9 Contraception advice

Women on buprenorphine should be provided with advice regarding contraception as part of routine care when commencing opioid treatment and on an ongoing basis during treatment (see Section A.4.2 and A.7. of Drug misuse and dependence: UK guidelines on clinical management [6]).

3.5.10 Pregnancy, breastfeeding and neonatal opioid withdrawal syndrome

Drug misuse and dependence: UK guidelines on clinical management state that BPN remains an option for pregnant women who have already been initiated onto BPN with informed consent, but that pregnant women should not be initiated onto BPN due to potential risks of opioid withdrawal in the foetus [6]. Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus [1 2]. BPN and methadone treatment, provided with adequate antenatal care, are associated with reduced maternal heroin use, reduced fetal death, increased neonatal birth weight and decreased premature delivery [16 17].

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

- higher than average sustained maternal blood levels of BPN than typically seen with SL BPN treatment
- excipients in monthly Buvidal®.

The individual risk and benefits of continuing any medication, should be considered during pregnancy. Pregnant women on depot BPN may be transferred to SL BPN. However, there may be clinical situations where pregnant women may not easily transfer to SL BPN (e.g. lack of access to daily sublingual treatment dosing) or it may be assessed that a pregnant woman is more likely to remain stable on depot BPN rather than transferring to sublingual treatment (i.e. the risks of transfer to sublingual treatment may outweigh the expected benefits).

N-methyl-2-pyrrolidone (NMP) is an excipient in monthly Buvidal®. The levels of NMP in monthly Buvidal® are less than the threshold for listing in this schedule (i.e. less than 25% of the product).

Whilst the mutagenic potential of NMP is weak, there is preclinical evidence of toxicity of NMP in rats and other animals, including decrease in foetal weight. A dose response effect in preclinical studies is noted, with adverse effects not being reported at lower NMP levels. In animals models the no observed adverse effect level was 160 to 237 mg/kg body weight, depending on route and species[18].

There is a lack of human data on exposure to NMP during pregnancy. There is a single case report of NMP exposure during pregnancy in a laboratory technician. The technician had repeated daily inhalation exposure to NMP from early pregnancy with direct dermal contact through a solvent spill at week 16. At week 20 intrauterine growth restriction was noted. At week 31 the technician delivered a stillborn baby. It is not possible to establish a causal relationship of NMP exposure during pregnancy and the stillbirth in this case [19 20 21].

Buvidal® has been approved for use in pregnancy by the European Commission where benefits outweigh the risks. The use of weekly or monthly formulations will be based upon individual clinical decision-making, which should include patient information and involvement [1 2].

3.5.11 Neonatal withdrawal

NAS is an expected and, potentially life-threatening outcome (if not screened for, or treated) of prolonged opioid exposure during pregnancy. Advise pregnant women receiving opioid treatment with depot BPN of the risk of NAS and ensure that appropriate treatment will be available as the onset and duration of neonatal withdrawal may be longer (e.g. 24 to 48 hours after expected onset with SL BPN).

Table 2: List of Depot BPN excipients

Excipient	Weekly Buvidal®	Monthly Buvidal®
soy phosphatidyl choline [soybean]	Yes	Yes
glyceryl dioleate	Yes	Yes
anhydrous alcohol	<100mg	
N-Methylpyrrolidone		57-114mg

While there is no further neonatal BPN exposure following delivery, foetal BPN exposure up until delivery may be higher than seen with SL BPN due to the different pharmacokinetic profile of depot BPN. Liaison with neonatologists / specialist pediatricians should occur regarding screening and treatment for NAS for neonates exposed to depot buprenorphine during pregnancy. It may be appropriate for clinicians to monitor neonates for a longer period than seen with SL BPN exposure, due to the different formulations.

3.5.12 Breastfeeding

Breastfeeding whilst being prescribed Buvidal® is listed as a caution in the SPCs [1 2]. Plasma levels of BPN seen with depot treatment are generally sustained over the weekly or monthly dosing interval with depot compared to the concentrations with SL BPN which fluctuate based on the daily dosing interval. However it is not anticipated that this will result in significantly higher BPN levels in breastmilk. While there is not a substantial literature regarding BPN exposure in infants due to breastfeeding [22] the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for depot BPN treatment and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Breastfeeding for mothers on BPN is encouraged, even if the mother continues to use drugs, except where she uses cocaine or crack cocaine, or a very high dose of benzodiazepines [6]. Breast feeding may reduce the intensity and length of NAS and has been shown to improve outcomes.

3.5.13 Drug–drug interactions (DDIs)

A number of potentially clinically relevant DDIs exist with BPN [1 2]. The SPCs for Buvidal® indicate:

- interactions with other opioids (precipitated withdrawal, blockade effects)
- interactions that increase the risk of overdose, as occurs with alcohol, other opioid drugs, benzodiazepines, tricyclics antidepressants, sedating antipsychotics and antihistamines) or through reductions in hepatic metabolism (Cytochrome P450 interactions) resulting in increased BPN plasma levels.

Many of these DDIs are difficult to predict in advance, and generally require clinical monitoring and dose adjustment. However, the prolonged duration of effects of the depot BPN formulations makes sudden cessation of BPN and/or titration of BPN doses more difficult than when using SL BPN. More stable BPN plasma concentrations experienced with depot formulations may make dosing of other medication easier, particularly given the lack of first pass/ hepatic metabolism with Buvidal® vs SL buprenorphine. If there are significant concerns regarding the clinical impact of DDIs, a period of treatment with SL BPN or switching to an alternative OST is recommended.

A detailed list of BPN interactions is available in the Drug misuse and dependence: UK guidelines on clinical management (appendix A5) [6] and the SPCs for Buvidal® [1 2]. For a list of DDI see appendix 3.

4 Providing treatment with depot BPN

4.1 Selecting treatment options

Opioid dependence is rarely an isolated problem and often co-exists with other harmful patterns of substance use (e.g. cocaine often as crack, alcohol, benzodiazepines, cannabis, tobacco), and other medical, psychiatric and social problems. Addressing these issues involves a coordinated treatment approach with other health and social service providers over an extended period.

OST has over many years been demonstrated to be a safe and effective treatment for addressing opioid dependence and provides the opportunity to engage patients with other health and psychosocial interventions. The key elements of OST are:

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

Drug misuse and dependence: UK guidelines on clinical management [6] state that methadone and buprenorphine are both effective medicines for maintenance treatment for heroin dependence, particularly when taken within the optimal dose range and that currently, there remains insufficient evidence to justify recommending one drug over the other. Furthermore, they state dose induction should aim carefully and as soon as possible for a stable dose of opioid that avoids both intoxication and withdrawal and a key goal of OST is to provide a dose that leads to complete cessation of heroin (or other illicit opioid) use. They refer to the fact that there is a very substantial evidence base supporting use of either of these drugs and it is appropriate for clinicians to discuss these complex issues with patients in obtaining informed consent for their treatment. This advice would apply equally when depot BPN is being considered as a treatment option.

Conventional OST with methadone and SL BPN treatment usually involves frequent initial attendance for titration and daily supervised dispensing from a pharmacy providing the opportunity to schedule regular clinical reviews, medical appointments and psychosocial interventions (e.g. counselling) and this has been a well-established treatment model in the UK for many years. However, treatment with depot BPN formulations potentially challenges the way in which the traditional components of OST services are coordinated and structured.

The less frequent dosing with depot BPN formulations may require a different approach to structuring clinical reviews, psychosocial interventions and treatment care planning. Despite the reduced frequency of medication administration, it should be emphasised that safe and effective OST is more than the provision of medication, and that regular reviews, treatment planning, and psychosocial interventions are equally important elements of OST.

It is possible to commence OST with weekly or monthly BPN formulations. Even though monthly BPN formulations are intended for 4 weekly injection intervals, clinicians may aim to schedule more frequent clinical reviews for patients initiating OST or during periods of clinical instability, during which assessment, care planning activities and psychosocial interventions can be scheduled. These issues should be discussed with individual patients when considering the choice of depot versus SL BPN treatment, and when developing treatment plans with patients.

Depot BPN treatment is indicated for treatment of opioid dependence within a framework of medical, social and psychological support. In this context medical support may be provided by a medical practitioner (general practitioner, addiction medicine specialist, addiction psychiatrist or other medical practitioner) in conjunction with other clinical staff (e.g. nursing staff) providing depot medication injections.

Social and psychological support may be provided by medical, nursing and/or other staff (including drug and alcohol workers, pharmacists, psychologists and other disciplines) depending on patient needs and the resources available.

4.2 Assessment and treatment planning

A comprehensive assessment is an essential component of safe and effective treatment, and aims to identify the pattern of substance use, key medical, psychiatric and social complications, and examine patient treatment goals and preferences. It may take several appointments to complete the assessment. Details regarding assessing patients for OST are described in Drug misuse and dependence UK guidelines on clinical management [6].

Treatment planning needs to involve the patient, taking into account their preferences and risks such as risks of diversion, accidental ingestion by children or others, and case complexity. It also 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, documented and be made available to the patient.

Informed consent is important in this area of healthcare. Patients should understand the implications of different treatment options, including potential risks and benefits, side effects, and other commitments. Use of depot BPN formulations has some additional factors compared to oral methadone or SL BPN to be taken into account given the long-lasting nature of the medication and its opioid blockade effect. This may have implications for instance should acute pain relief be required. Patients should be provided with written information, and opportunities to ask questions regarding treatment options. Alternative communication methods may be required for patients with cognitive impairment, language and cultural factors.

4.3 Patient and clinician factors in choosing depot BPN compared with other OST options

There can be little doubt given the research evidence and long-established clinical experience that both methadone and BPN are safe and effective in the treatment of opioid dependence [6 23]. Key factors in choosing between methadone and BPN medications are described in Drug misuse and dependence: UK guidelines on clinical management [6]. These include patient factors such as prior experience with medications, adverse events, drug interactions, overdose risks, and in some cases logistic factors such as access to supervised dispensing and physical disabilities, where more flexible dosing options may be preferable.

Where a decision is made in conjunction with the patient that BPN would be the most appropriate medication there is minimal research evidence to guide decisions regarding the choice between the depot BPN formulations (weekly or monthly Buvidal®) and SL BPN treatment, and individual patient and clinician factors need to be considered.

5. Guideline regarding dosing regimens with depot BPN

5.1 Transitioning from SL BPN treatment to depot BPN

Patients treated with SL BPN formulations may be transitioned directly to Buvidal® prolonged-release injections starting on the day after the last daily SL treatment dose (see conversion recommendations in Table 1). Individual clinical titration of doses may be required on subsequent doses, recognising that the dose effects of the depot formulations are likely to increase with BPN accumulation until steady state equilibrium is achieved (usually after 4 doses).

Factors that may lead to the clinician and patient choosing weekly over monthly treatment may include: desire for more frequent clinical review or concomitant use of benzodiazepines, alcohol or other sedatives or if the patient presents with mild to moderate hepatic impairment.

Table 1: Dose conversions between SL BPN, depot weekly Buvidal® and monthly Buvidal® doses [1 2 3 4 5]

Dose of daily sublingual buprenorphine	Dose of daily Espranor® ⁎	Dose of weekly Buvidal®	Dose of monthly Buvidal®
2-6mg	2-4 mg	8mg	
8-10mg	6-8mg	16mg	64mg
12-16mg	10-12mg	24mg	96mg
18-24mg	14-18mg	32mg	128mg

⁎ 25-30% higher bioavailability for Espranor® than for sublingual Subutex® tablet

NB Different BPN products have different maximum doses.

5.2 Initiating directly to Buvidal®

Depot BPN should be started when objective and clear signs of mild to moderate withdrawal are evident. A validated tool such COWS scale can be used to support this assessment (e.g. COWS score of 10 or more). Clinicians should monitor levels of withdrawal so that the patient does not become too uncomfortable (CS). For patients who have not previously been exposed to BPN a SL BPN test dose should be given prior to the administration of a weekly Buvidal® prolonged-release injection to confirm tolerability to BPN. The recommended starting dose of Buvidal® for patients not previously receiving BPN is 16 mg, with one or two additional 8 mg doses at least 1 day apart. The recommended dose for the second treatment week is the total dose administered during the week of initiation. A clinical decision may be made that a test dose is desirable to reduce the risk of precipitated withdrawal in patients who are not already receiving BPN (CS).

5.3 Titrating doses of Buvidal®

Patients transferred directly to monthly Buvidal® can usually continue on the conversion dose without experiencing cravings, withdrawal symptoms or reporting significant heroin or other non-prescribed opioid use. Four doses are required to achieve steady-state plasma levels.

For patients initiated onto weekly Buvidal® in week 1, the recommended dose for the second treatment week is the total dose administered during the week of initiation. Treatment with monthly Buvidal® can be started in accordance with the dose conversion information in Table 1 once patients have been stabilised on weekly treatment.

5.4 Key principles in titrating depot BPN doses – adjusting dose and frequency of doses (CS)

In general, doses should be maintained if:

- the patient is achieving key treatment outcomes, such as no unsanctioned use of opioids, and 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 is requesting the dose be maintained.

Doses should generally be reduced under the following conditions:

- the patient reports BPN dose-related adverse events (e.g. sedation or lethargy, persistent headaches, nausea, elevated liver function tests)
- the patient is seeking to reduce the dose in an attempt to ultimately withdraw from OST
- 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
- the patient is using other non-opioid CNS depressants which may increase their risk of opioid overdose.

Dose should generally be increased under the following conditions:

- the patient is not achieving desired treatment goals (e.g. persistent unsanctioned opioid use, opioid withdrawal symptoms or cravings)
- the patient does not report dose-related adverse events related to BPN (e.g. sedation or lethargy, persistent headaches, constipation, nausea, elevated liver function tests)
- the patient reports their dose is too low and they would like a dose increase, and there are no significant clinical safety concerns.

The maximum dose per week for patients on weekly Buvidal® is 32 mg with an additional supplementary 8 mg dose (i.e. 40 mg). The maximum dose per month for patients on monthly Buvidal® is 128 mg with an additional supplementary 8 mg dose (i.e. 136 mg).

5.5 Switching between weekly and monthly Buvidal® (CS)

Patients may be switched from weekly to monthly dosing or from monthly to weekly dosing based on the recommendations in Table 1 (section 5.1). The SPCs recommend that patients can be switched from weekly to monthly Buvidal® after 4 weeks of treatment. In some instances, clinicians may consider switching sooner based upon an assessment of broader risks and overall treatment benefit (for example retention in treatment and/or patient wishes). Titration to higher or lower doses may be required. Patients switching from weekly to monthly dosing will generally experience trough levels in the first few months similar to patients switching from SL BPN. Patients should be monitored for increased withdrawal or craving symptoms or other signs of instability.

Titration of Buvidal® may be desirable if patients present with significant opioid withdrawal during the first three to four doses of Buvidal® whilst steady state plasma levels are being reached. Buvidal® should be administered weekly or monthly according to individual patient need and clinical judgement and at doses established after initiation or switching.

5.6 Buvidal® flexible dosing schedules and supplemental BPN dosing (CS)

Top-up or supplemental doses of Buvidal® may be given if the patient experiences clinical features of opioid withdrawal, cravings or persistent unsanctioned opioid use. In general, treatment with depot BPN should not routinely require additional or supplemental BPN dosing. Wherever possible, depot doses should be adjusted to ensure that patients are effectively and safely treated. However, there may be instances where supplementary doses are required. Examples include:

- during dose titration in the early stages of depot treatment. For example, depot BPN doses are adjusted according to the patient's prior dose, however, these transitional doses are a guide only, and subsequent dose adjustment may be required. Supplemental BPN doses may enable the patient to be held over until their next scheduled depot dose.
- following drug-drug interaction – the commencement of another medication that induces hepatic metabolism of BPN (e.g. CYP 3A4 inducer such as carbamazepine) may cause BPN plasma levels to be reduced – resulting in features of opioid withdrawal, cravings or unsanctioned drug use.
- delayed or interrupted depot dosing. Patients may miss their routine dose of depot BPN due to unforeseen circumstances, such as travel, transport problems, or other commitments. In some cases, a dose of depot BPN can be organised. However, in some cases patients may not be able to access their routine depot dose on time and interim period of treatment with SL BPN may be appropriate, given it is more widely available in a range of community settings than depot products.

If clinically indicated, a maximum of one supplemental Buvidal® 8mg dose may be administered at an unscheduled visit between regular weekly and monthly doses. The maximum dose per week for patients who are on weekly Buvidal® treatment is 32mg with an additional 8mg dose (i.e. 40mg). The maximum dose per month for patients on monthly Buvidal® is 128 mg with an additional supplementary 8 mg dose (i.e. 136 mg). There may be circumstances where supplemental doses of BPN are required but weekly Buvidal® 8mg doses are not possible to administer (e.g. travel away from regular service providers). Supplemental low doses of SL BPN (e.g. 4mg or 8mg) may be used for a limited period of time until the next depot injection can be arranged (CS).

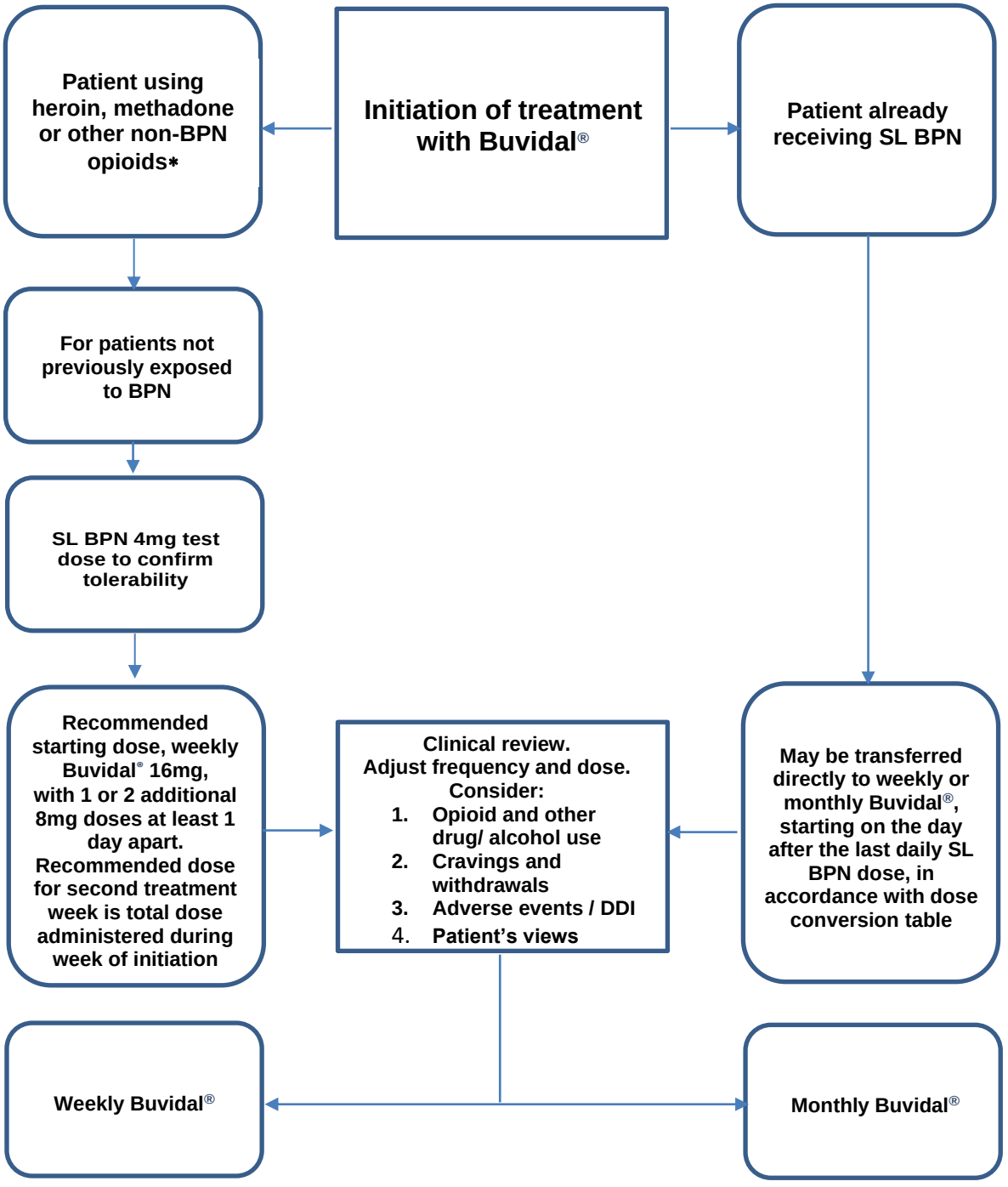
Whilst doses will be routinely scheduled to occur every 7 or 28 days, it is recognised that some flexibility is required to accommodate missed appointments, travel, public holidays, appointment availability etc. To avoid missed doses, the monthly dose may be administered up to 1 week before or after the monthly time point (weeks 3-5). The weekly dose may be administered up to 2 days before or after the weekly time point (days 5-9).

It should be emphasised that patients should not be maintained for more than 14 days on SL BPN treatment in addition to depot BPN doses. Adjustment of the next depot BPN dose is recommended. If patients persistently describe their depot BPN dose is not sufficient despite being on the maximum possible dose (e.g. monthly Buvidal® 128mg) then consider discontinuing depot treatment and resuming an alternative OST.

5.7 Outside Summary of Product Characteristics (CS)

If a dose is missed, the next dose should be administered as soon as practically possible. If more than eight weeks between monthly Buvidal® has elapsed, or two weeks between weekly Buvidal® has elapsed, re-induction may be required, with individual clinical titration (CS).

Dosing with Buvidal®



Dose conversion table

Dose of daily sublingual buprenorphine	Dose of daily Espranor®	Dose of weekly Buvidal®	Dose of monthly Buvidal®
2-6mg	2-4 mg	8mg	
8-10mg	6-8mg	16mg	64mg
12-16mg	10-12mg	24mg	96mg
18-24mg	14-18mg	32mg	128mg

* For patients using heroin or short-acting opioids, the initial dose of Buvidal should not be administered until at least 6 hours after patient last used opioids. For patients receiving methadone, the dose should be reduced to maximum of 30mg/day and Buvidal should not be administered until at least 24 hours after last methadone dose.

5.8 Induction from other opioids: prescription opioids and methadone

To avoid precipitating symptoms of withdrawal, treatment with Buvidal® should be started when objective and clear signs of mild to moderate withdrawal are evident. Consideration should be given to the types of opioid used (that is long- or short-acting opioid), time since last opioid use and the degree of opioid dependence.

- For patients using heroin or short-acting opioids, the initial dose of Buvidal® must not be administered until at least 6 hours after the patient last used opioids.
- For patients receiving methadone, the methadone dose should be reduced to a maximum of 30 mg/day before starting treatment with Buvidal® which should not be administered until at least 24 hours after the patient last received a methadone dose. Buvidal® may trigger withdrawal symptoms in methadone-dependent patients.

5.9 Administering Buvidal® injections

Buvidal® should be injected slowly, into the subcutaneous tissue of the buttock, thigh, abdomen, or upper arm. Each area can have multiple injection sites. Injection sites should be rotated for both weekly and monthly injections. A minimum of 8 weeks should be left before re-injecting a previously used injection site with the weekly dose. There is no clinical data supporting reinjection of the monthly dose into the same site. This is unlikely to be a safety concern. The decision to reinject at the same site should also be guided by the attending healthcare professional's clinical judgement.

The administered dose should be as a single injection and not divided. The dose must not be administered intravascularly (intravenously), intramuscularly or intradermally (into the skin). Injections on the waistline or within 5 cm of the naval should be avoided. The angle of injection will depend on the amount of subcutaneous tissue however Buvidal® should usually be administered at 90 degrees. For detailed instructions see appendix 4 and refer to weekly Buvidal® and monthly Buvidal® SPCs [1] [2].

5.10 Specific issues of delivering OST with depot BPN

5.10.1 Intoxicated presentations

Patients presenting intoxicated at the time of dose administration should be assessed to identify any safety concerns regarding dosing. Peak plasma and clinical effects occur 24 hours after weekly Buvidal®, and at 6-10 hours for monthly Buvidal® and hence there is usually little clinical indication to withhold a depot injection due to a patient presenting intoxicated, in contrast to intoxicated presentations for SL BPN or methadone dosing, where peak medication effects are likely to occur whilst the patient is still intoxicated. However, patients should be assessed as having capacity to provide informed consent to their usual dose, and to understand warnings regarding risks of sedation and overdose from polysubstance use. If there are concerns that the patient is very intoxicated and unable to understand or follow instructions, the administration of the dose may be deferred and rescheduled. Acute alcoholism or delirium tremens are contraindications.

5.10.2 Transfer of care

Particular attention is required when communicating with other healthcare providers regarding transfer of care for patients treated with depot BPN. Many healthcare providers may be unfamiliar with Buvidal® formulations, and its prolonged dosing intervals.

When transferring care or providing clinical handover to other healthcare providers, ensure the following is communicated clearly:

- details of service providers prescribing and administering depot BPN injections
- previous injection sites (in order to avoid injecting into same site)

- dose and date of recent depot BPNs ensuring details of last dose administered are included
- the formulation of depot BPN that was administered and the dose (in mg)
- scheduled next dose of depot BPN (formulation, date, dose strength and route of administration)
- any adverse events, risks or concerns regarding depot BPN treatment.

As depot BPN treatment is new, untrained service providers may be unfamiliar with the treatment model or doses used. Providers transferring care should ensure that differences in the doses, frequency of administration and dispensing conditions are understood by the new provider.

As depot BPN medication may not be easily administered during a brief inpatient hospital admission, it is possible that it may be erroneously omitted from hospital discharge summaries and medication reconciliation procedures. Treatment providers should endeavour to ensure that BPN treatment is accurately documented in transfer of care documentation and related clinical handover activities. Providers may consider the development of a template to support the safe transfer of care for the patient and a Standard Operating Procedure (SOP) outlining the process.

5.11 Prescription writing

Prescribers must ensure that all prescriptions for depot BPN are legally written, and compliant with the Misuse of Drug Regulations 2012. See Appendix A4 of Drug misuse and dependence: UK guidelines on clinical management (2017) for further details [6].

6 Discontinuing depot BPN treatment

6.1 Potential scenarios for discontinuing depot BPN treatment

Potential scenarios for discontinuing depot BPN treatment include:

- withdrawing off depot BPN (with goal of opioid abstinence)
- transfers to SL BPN
- transfer to methadone / other OST
- transfer to oral naltrexone.

6.2 Withdrawing off depot BPN (with goal of opioid abstinence)

Many patients in OST are keen to achieve not only abstinence from illicit drugs but also to discontinue opioid treatment and withdraw from all opioids. Drug misuse and dependence: UK guidelines on clinical management [6] state that in dependent opioid users, detoxification is usually a clearly defined process, supporting safe and effective discontinuation of opioids while minimising withdrawals. The process varies in duration from person to person, usually lasting about 28 days as an inpatient or up to 12 weeks as an outpatient. This reflects the main evidence base on detoxification, which informs good practice. Slower detoxification often does occur and is supported by clinicians but has a limited evidence base.

The assessment process can establish whether a patient is suitable for detoxification. It should be remembered that detoxification alone is rarely successful especially at the first attempt. Patients who do not successfully detoxify should be offered seamless access back into maintenance or other treatment. The following factors can guide the clinician's and patient's opinions about whether the patient is suitable for detoxification:

- the patient is fully committed to and informed about the process
- the patient is fully aware of the high risk of relapse
- the patient is either in a stable and supportive social situation or able to go into one following detoxification
- plans for continuing support and treatment are in place
- there is clear evidence that coerced detoxification against a patient's will is likely to lead to relapse and increased risks of harm such as overdose and blood-borne viruses.

There is currently very little experience and no studies examining withdrawal from depot BPN treatment. The withdrawal time course and severity has not been characterised for depot BPN products.
The onset, peak and duration of withdrawal symptoms may well be variable between patients, and is likely to be influenced by the duration of previous dosing of depot BPN. In general, the withdrawal syndrome from depot BPN is expected to occur several weeks to several months after the last dose, persist for longer, and may be of lower severity than withdrawal from SL BPN.

Patients who have been in treatment for long enough to achieve steady state plasma levels of depot BPN are likely to have a longer time course of reduction of BPN levels and therefore longer time course of withdrawal symptoms than those on depot BPN treatment for shorter periods.

Wherever possible, patients should reduce depot BPN dose prior to discontinuing dosing. For patients on monthly Buvidal® this could involve switching to the weekly preparation before ceasing depot BPN. It is generally recommended to taper the depot dose to the lowest possible before discontinuing treatment.

As in attempts to withdraw from other forms of OST, 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, however caution should be used in using extended use (beyond a few days) of sedatives or hypnotic medications. Given the risks of relapse, patients who have withdrawn from depot BPN should be supplied with take-home naloxone.

6.3 Transfers to SL BPN (CS)

Given the variable excretion and clinical effects of depot BPN products there can be considerable individual variation in when the clinical effects of prior depot BPN treatment subside. This will be affected by prior depot dose (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.

Initiate SL BPN dosing at the time of the next scheduled injection (e.g. 5-9 days after weekly Buvidal® and 3-5 weeks after last monthly Buvidal® injections). Dose conversion tables should be used to guide the initial SL BPN dose, with frequent clinical reviews in order to titrate the SL dose over subsequent days bearing in mind the variation in maximum doses for the various SL BPN products.

Table 1: Dose conversions between SL BPN, depot weekly Buvidal® and monthly Buvidal® doses [1 2 3 4 5]

Dose of daily sublingual buprenorphine	Dose of daily Espranor® ⁎	Dose of weekly Buvidal®	Dose of monthly Buvidal®
2-6mg	2-4 mg	8mg	
8-10mg	6-8mg	16mg	64mg
12-16mg	10-12mg	24mg	96mg
18-24mg	14-18mg	32mg	128mg

⁎ 25-30% higher bioavailability for Espranor® than for sublingual Subutex® tablet

NB Different BPN products have different maximum doses.

It should be emphasised that there remains a relative lack of experience in transferring patients from depot to SL BPN and faster response times, or higher or lower doses than those suggested above may be required. Patients should be reviewed regularly, and doses titrated according to clinical need, and clinicians should document the rational for their decision-making.

6.4 Transfer to methadone or other opioid analgesics (CS)

There is currently little clinical experience and no published studies regarding transfer from depot BPN to methadone. Given this lack of evidence, it is suggested that patients seeking to transfer from depot BPN to methadone should transition via SL BPN. Once stabilised on a dose of SL BPN for at least 4 weeks then transition to methadone can occur. However, it is recommended to initiate at low doses (20-30mg daily), reviewing regularly and titrating accordingly.

If a patient has to discontinue all BPN treatment abruptly (e.g. due to a severe adverse event, or patient unwillingness to continue any BPN treatment), transition to methadone can be considered. The general principle is to commence low dose methadone (e.g. 20mg oral daily doses) at the time of the next proposed depot dose, regularly monitor the patient (at least weekly), and carefully increase the dose (by no more than 5-10mg increments after clinical reviews until the methadone dose and patient have stabilised, recognising that residual BPN from depot BPN doses may be present for up to 4-6 months after long term treatment with Buvidal®.

6.5 Transfer to oral naltrexone (CS)

Following cessation of depot BPN, transfer to oral naltrexone is feasible after BPN effects have subsided, typically 2-4 weeks after weekly depot BPN 4 to 12 weeks after the last dose of monthly depot BPN. However 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 ideally a negative naloxone challenge. A test dose of 25mg should then be given on day 1 and then if no precipitated withdrawal or adverse reactions are experienced a maintenance dose of 50mg daily should be prescribed in line with current UK practice. Given that this is likely to be used in a very small number of patients, consultation with a specialist is recommended if there are any concerns.

7 Clinical conditions

7.1 Overdose

Whilst BPN on its own is rarely associated with overdose in dependent opioid users, overdose can occur in the context of polydrug use, specifically the use of other sedatives such as alcohol and benzodiazepines. Under such circumstances, emergency treatment is required with supportive care (oxygen therapy, assisted breathing and recovery position) and the use of naloxone. Whilst laboratory studies (animal and receptor binding studies) suggest that very high doses of naloxone (e.g. 10mg IM/IV) are required to reverse the effects of BPN (due to the comparable affinity of BPN and naloxone for the mu opioid receptor), in practice, polydrug overdoses in which BPN is implicated generally respond to routine doses of naloxone (e.g. 1-2mg IM/IV).

The specific potential risks of the depot BPN product are the prolonged plasma levels of BPN, rather than higher plasma levels compared to sublingual dosing, hence there may be no greater risk of overdose occurring from depot BPN formulations. However the prolonged duration of depot BPN formulations requires patients to be clinically monitored for extended periods of time, until the patient has recovered, and may require prolonged monitoring and a naloxone infusion in a hospital setting. Note that depot BPN Buvidal® must be administered as a subcutaneous injection.

7.2 Polydrug use and regular intoxication

The issue of administering depot BPN doses to an intoxicated patient is addressed in section 5.10.1. Specific interventions may be required for patients with harmful patterns of substance use of other drugs, such as alcohol, benzodiazepine, stimulants, cannabis and/or injecting drug use. These are described in Drug misuse and dependence: UK guidelines on clinical management [6].

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, then a medication option with a more frequent dosing interval may be considered. Patients with heavy and regular/ dependent patterns of use of alcohol, benzodiazepines and stimulants (and other psychoactive substances) may require specific psychosocial interventions aimed at reducing/ceasing use of those substances.

7.3 Acute pain management in patients in depot BPN treatment

Patients on opioid agonist treatment can encounter episodes of acute pain that require management, which can be complicated by BPN treatment. Nevertheless, there are evidence-based approaches for pain management and it is important that patients have access to effective pain management.

BPN has high mu receptor affinity and reduces the effects of most full opioid agonists such as morphine or oxycodone. Whilst this has little impact on the management of mild acute pain (where NSAIDs or paracetamol and physical therapies may be considered), BPN can complicate routine opioid analgesia in the management of severe acute pain (e.g. in acute/emergency situations such as trauma, renal stones). It is important that patients' acute pain is effectively managed and in such circumstances, Drug misuse and dependence: UK guidelines on clinical management [6] recommend the following approaches:

- use of higher doses of traditional opioids such as morphine (with careful titration of effects)
- use of mu opioid receptor super agonists such as fentanyl that themselves have higher mu intrinsic activity than BPN; and/or
- use of non-opioid analgesic approaches such as ketamine infusions or regional analgesia.

Similar approaches can be used for patients with depot BPN treatment to achieve analgesia in acute/emergency situations. It is not possible to reverse or cease BPN plasma levels in patients treated with depot BPN formulations.

7.4 Chronic pain management in patients in depot BPN treatment

Chronic pain is common amongst patients on OST 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 and include patient education and engagement in the treatment process, appropriate use of opioid and non-opioid medications (e.g. antidepressants, NSAIDs, paracetamol,), physical (e.g. exercise, physiotherapy) and psychosocial (e.g. Cognitive Behavioural Therapy) interventions [6].

BPN itself is a powerful opioid analgesic, and extended-release BPN formulations (e.g. 7-day topical patches) have historically been incorporated into treatment plans for patients with concurrent chronic pain, and it is possible that depot BPN formulations may also be effective as part of treatment plans in managing comorbid chronic pain in dependent opioid users. There is no evidence currently available evaluating high dose sublingual and depot BPN formulations in chronic pain management.

8 Use of depot BPN for withdrawal treatment

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 or methadone, given their long duration of action, gradual taper of BPN plasma levels, and logistic simplicity (e.g. one single dose without need for daily dosing). The gradual taper over days (for weekly Buvidal®) or weeks (monthly Buvidal®) may be well suited to assisting patients attempting opioid withdrawal.

However, at this time there is little clinical experience or research evidence to inform the use of depot BPN for managing opioid withdrawal, and further research is required. Consultation with a suitable addiction specialist prescriber is recommended.

9 Special populations and settings

9.1 High risk or vulnerable populations

There are a range of health conditions (e.g. cognitive impairment, severe psychiatric conditions, poor mobility), social circumstances (e.g. safeguarding concerns, domestic violence, homelessness, poor literacy, social isolation) and demographics (culturally diverse backgrounds, women, LGBTQ+ people, culturally diverse communities, prisoners, older people) that can greatly impact upon the experience of engagement of patients with opioid treatment (and other service) providers. The introduction of depot BPN treatment allows for dosing on a weekly or monthly basis and may enhance patient autonomy in some cases; alternatively it may detract from the ability to engage the patient with treatment and other services. Particular attention to informed consent to treatment with depot formulations is required, and advocacy services should be available. Service providers and patients should collaboratively implement strategies that aim to enhance attendance for dosing and clinical reviews and consider active follow-up strategies for patients who do not attend for scheduled appointments. This is a particular challenge when shifting from daily dispensing of medication which may be supervised. The risk of loss of contact with the patient needs to be weighed up against the risk of missed doses, poor compliance with medication or even complete disengagement with the treatment process if SL BPN is not considered.

Protection of vulnerable patients who are opioid dependent can result in serious challenge. Patients who are being exploited, or are in domestically violent settings, or on witness protection programs often require flexible, responsive and rapid treatment approaches to stabilise opioid dependence while often considering a geographical move to a place of safety. The option to rapidly induct a patient onto a long-acting preparation offers a window of flexibility for other services such as police, social services and housing charities to work to remove the patient from danger whilst not disrupting or jeopardising OST.

9.2 Hospital and secure environment settings

Many patients in OST have brief episodes of admission to hospital or secure environment settings (e.g. prison) that result in interruptions in methadone or BPN dosing. It is expected that this will be less of a concern with depot BPN treatment, nevertheless, in this situation careful co-ordination between hospital and secure environment settings will be required.

During acute admission in hospital settings coexisting opioid dependence and associated withdrawal symptoms, or drug seeking and taking behaviour can undermine the admission, resulting in patients taking their own discharge against medical advice, or demonstrating behavior that is disruptive and difficult to manage in an acute care setting. Attempts to provide rapid stabilisation of opioid dependence are often made to support the patient in being able to sustain the admission. Methadone or SL BPN are both options in this situation, however depot BPN may provide an alternative with significant advantages due to its weekly and monthly administration, and it may also provide a degree of protection against overdose if a patient does leave abruptly without securing onward prescribing. Management of acute pain will have to be considered on a case-by-case basis in respect of the interaction between BPN and full opioid receptor agonists. Benefits of BPN in acute care settings include its relatively low risk of respiratory depression and sedation compared with full opioid agonists.

Police custody settings also present a unique challenge in managing opioid dependence and withdrawal symptoms, and also in ensuring continuity of OST. Often patients are detained for short periods of time, outside of usual working hours and with limited access to prescribing services. There are a number of factors which influence which, if any, treatments are offered for acute amelioration of acute opioid withdrawal, and whether or not the patient will have access to daily supervised doses of OST.

Patients who are maintained on depot BPN preparations should present less of a challenge in these settings due to weekly or monthly administration with a window of flexibility around dosing days making it relatively straight forward to maintain treatment continuity which, in turn, improves patient safety.

9.3 Secure environment settings

Depot BPN has a number of potential benefits as a treatment option in secure environment settings. Diversion of SL BPN is commonplace in prisons and is associated with interpersonal violence as well as viral and non-viral injecting-related injuries and diseases. Within the UK prison estate, insufflation is a common method of abusing BPN. Diversion and misuse of SL BPN in the UK HMP estate is endemic, and there is evidence that supply and distribution is organised with significant financial implications. Reports of debt, bullying and assault are commonplace and have significant costs, both to the individual, their family and also across the secure estate. Depot BPN formulations have less capacity for diversion and compliance is easier to ensure. Individuals who receive effective BPN treatment are unlikely to engage in BPN abuse, therefore reducing demand for illicit products.

Administration of SL BPN in prisons is time-intensive, with individual patients taking 10-20 minutes for SL formulations to dissolve, requiring considerable time resources for both prison officers and health staff. Novel lyophilisate preparations do dissolve more rapidly, reducing supervision time, however they do not remove the requirement for staff to supervise daily doses. Once-a-month administration of depot BPN will allow increased time for patients to receive other health interventions. Depot BPN can also be delivered in secure environment healthcare settings, removing the risk of bullying that can result from patients having to disclose their treatment to other inmates.

The period immediately following release from custody is a high-risk period for patients, with significant risk of overdose and death. It is widely accepted that enforced periods of abstinence from opioids whilst in custodial settings results in loss of tolerance and a significant increased risk of fatal overdose if opioid use is reinstated on release. Evidence suggests that provision of OST within HMP and on release results in a 75% reduction in all-cause mortality and an 85% reduction in mortality from opioid overdose in the first month following release [24]. HMPs have responded to this risk by offering a wide range of OST options within the secure setting that should reflect a degree of equivalence with community services, and also by offering re-titration onto OST prior to release. However there is variation in provision throughout the secure estate and many challenges to providing smooth transition of prescribing on release. Unexpected release from court, or short sentences can present challenges including the timely identification of a community prescriber, and issues with complexity of social situation can interfere with patients' engagement with community providers during the transition period. A depot preparation may provide greater stability over this period with less urgency for immediate attendance at community clinic or pharmacy. This may be beneficial for both the patient and community treatment teams.

Patients on depot BPN leaving custody should be provided education regarding the persistent clinical effects and duration of depot BPN.

As depot BPN may take several doses to reach steady state, transfer of care documentation both on entry into custody and on release will require detailed documentation of doses given over a period several months.

There is a need for flexibility in transferring between depot BPN and oral OST, in case availability is not consistent across settings. It is straightforward to transition between SL and depot BPN, and if needed, patients can be transferred from depot to SL BPN when the next depot dose is due, at an equivalent dose. Transferring to a full opioid agonist such as methadone will not be as straightforward, due to the extended wash out period of depot BPN, and therefore there is potentially reduced effectiveness of methadone for an extended period following depot BPN administration.

9.4 Residential rehabilitation and supported housing settings

There are a variety of community residential settings that can provide challenges for maintaining patients on OST. Supported living projects are becoming increasingly common in the UK. They are often faith-based and are not included under the residential rehabilitation frameworks. As housing-based projects they do not require registration as care homes and do not have facilities for managing or dispensing controlled drug medications on site. Many aspire for patients to be abstinent from prescribed opioids, but this may in part be due to the challenges of supporting patients to attend for daily supervised medications, and also due to the problems associated with introducing opioid medications such as methadone or SL BPN into their setting. The risk of patients living in supported living projects relapsing following either planned or unplanned exit is high, with the associated increased risk of overdose due to loss of tolerance. Depot BPN may provide an option for patients to be maintained on OST during extended stays in therapeutic communities, removing any requirement for medication storage on site and pharmacy attendances.

Most residential rehabilitation units in the UK are abstinence based in their approach, and would usually expect patients to be opioid free, or undergo detoxification prior to fully engaging in an inpatient rehabilitation program. This does create a barrier for many patients who are not ready for abstinence. Some units will consider an integrated approach, allowing patients to remain on OST, and depot BPN may provide an opportunity to have a bridge between OST and recovery, further integrating the patient journey through medically assisted recovery.

By moving away from a daily dosing structure of a medication which has significant abuse potential, to a preparation which is administered weekly and monthly, and achieves consistently stable plasma levels between doses, patients and treatment providers can start to explore the complex relationship between chemical dependence and addiction. A more flexible approach for delivering bespoke recovery care options could support a holistic and integrated model of medically assisted recovery.

Treatment with depot BPN should be delivered within a framework of comprehensive assessment of the patient's chemical dependence, general health, social functioning, and should be underpinned by regular reviews with a keyworker [6].There are specific aspects of depot BPN treatment that will need to be addressed:

- adapting delivery of ongoing support and connection, especially if the patient is moving from very regular contact with a service due to removal of daily supervised medication
- encouraging patients to think about how they will fill their time positively, in a way that helps them move forward, become healthier and improve self-esteem
- making sure patients have access to the patient leaflets for Buvidal®.

Clinicians considering depot BPN treatment should be sensitive to the diversity of patients including:

- being aware that some cultures will have restrictions around the gender of the person who can give them an injection.
- being aware that there may be cultural issues around injecting in particular sites.
- understanding that using a professional interpreter is always preferable to using a family member, for clearer, unbiased and confidential exchange of information.

All in all, the best therapeutic relationships are built on co-operation, unbiased information sharing and an honest and open exchange that balances clinical responsibilities with the patient's treatment goals.

9.5 Managing travel

Patients must not be supplied directly with Buvidal®. Depot BPN must only be handled by a healthcare professional prior to administration. BPN must only be handled by a healthcare professional after delivery to a clinic/administration site or collection from the community pharmacy by a healthcare professional or practitioner from the drug service provider.

9.5.1 Local travel

The duration of action of depot BPN should make local travel less problematic for patients. For information on doses that need to be given before/after the scheduled date see section 5.6.

9.5.2 Overseas travel

Weekly Buvidal® cannot be given to patients for overseas travel for more than 9 days and for monthly Buvidal® if the travel duration is more than five weeks. Patients wishing to travel abroad for longer periods may have to be transferred back to SL BPN. Dose titration of the required sublingual dose should occur before travel commences so patients can be observed during transfer from depot BPN to SL BPN.

10 Patient information and perspective

Depot BPN should always be presented as one choice in the range of available OST medications. Patients may need a great deal of information and reassurance from clinicians as they assess whether depot BPN will be compatible with their lifestyles and where they are in their treatment journeys. This support will need to continue if a patient decides to receive depot BPN treatment. No matter the advantages of the new formulation, the depot injection is a leap in the dark that for many patients will signify a relinquishment of control, and also a significant change from the routine of daily attendance for dosing.

There will be patients who wish to transition to depot BPN who are currently in treatment on both sublingual BPN and also methadone. All patients will need to know how depot BPN medication is similar to, and different from, the formulation they are currently taking, and what is involved in transitioning.

The decision-making process and initiation or transitioning phase should occur within a co-operative therapeutic relationship that balances a clinician's medical expertise and knowledge and with a patient's treatment goals.

Patients need to be supplied with a wide range of information about depot BPN. Patients may want to know about:

- product pharmacology profile, effectiveness and safety including half-life and average peak/trough patterns, control of cravings
- prescribing and dosing procedures including dose amounts, duration of effect and dosing schedule
- the way transfer from other OST medications will take place and if they will experience withdrawal symptoms
- options for managing side effects, chronic and acute pain and exiting the program
- any other problems that might arise and how they might be addressed
- their rights and responsibilities.

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As a clinician, patient agency and choice can be enhanced by:

- recognising that depot BPN will suit some but not all people currently in treatment, or considering entering treatment and that a choice of a range of OST medications is an essential health response
- listen to, take seriously and act promptly when patients describe their experience – including subjective feelings of opioid withdrawal or cravings to use opioids
- encouraging patients to compile a list of advantages and disadvantages to help with decision-making
- offering a move to depot BPN as a trial, reassuring your patient that they will be able to return to sublingual BPN or methadone if depot BPN does not suit them
- respecting a patient's decision to not try depot BPN, no matter what their reasons are
- making sure the patient has sufficient harm reduction information if they do not want to be abstinent from all illicit drugs, with special attention to overdose risks and reversal.

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

11 Buvidal® and the DVLA

Doctors and other healthcare professionals should:

- advise the patient on the impact of their medical condition for safe driving ability
- advise the patient on their legal requirement to notify the DVLA of any relevant condition
- treat, manage and monitor the patient's condition with ongoing consideration of their fitness to drive
- Notify the DVLA when fitness to drive requires notification but an individual cannot or will not notify the DVLA themselves
- the DVLA guidance does not make specific reference to depot BPN but outlines the current guidance for patients on oral methadone or BPN. Chapter 5 of the DVLA guidance and should be adhered to under usual situations [25].
- the DVLA guidance will require updating in line with the new depot treatment formulations available. In the interim, it is advised that prescribers of Buvidal® apply the existing guidance which is to advise patients that they must not drive, and that they must notify the DVLA of their medical condition and the medication prescribed
- the SPCs for Buvidal® state that buprenorphine has minor to moderate influence on the ability to drive and use machines when administered to opioid-dependent patients. Buprenorphine may cause drowsiness, dizziness or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or other central nervous system depressants, the effect is likely to be more pronounced. The patient should be cautioned not to drive or operate hazardous machinery whilst taking this medicine until it is known how the patient is affected by the medicine. An individual recommendation should be given by the treating healthcare professional.

12 Governance

12.1 Acquisition

Buprenorphine is considered a controlled Class C drug under the 1971 Misuse of Drugs Act [26]. As such, it is subject to the Misuse of Drugs (Safe Custody) (Amended) Regulations 2007 [27] detailing requirements for supply and possession in the UK. Buprenorphine sits in schedule 3 of the regulations. It is subject to special prescribing and safe custody requirements.

Prescriptions can be written on FP10, for dispensing to a healthcare professional to be administered in service or for administration by a suitably qualified community pharmacist where a Patient Specific Directive is in place.

Buvidal® can be ordered by a service direct from a wholesale supplier where the service is in receipt of a Home Office license for the purchase of controlled drugs.

12.2 Storage

Buvidal® injections have no special precautions listed for storage in the SPCs except that the product should not be refrigerated or frozen.

As a Class C schedule 3 controlled drug, safe custody is required when storing Buvidal®. This applies when healthcare professionals are transporting medication from the pharmacy and storing in clinic facilities on a temporary basis [28].

12.3 Accountability

There is no legal requirement to keep a Controlled Drug Register for Buvidal®. However, it is good practice to keep a log of stock for transparency and audit purposes.

Buvidal® administration should be recorded clearly within the patient records and include:

- name and date of birth of the person having the dose administered
- date and time of the dose
- name, formulation and strength of the controlled drug administered
- dose of the controlled drug administered
- name and signature or initials of the person who administered the dose
- name and signature or initials of any witness to administration
- the Batch Number and expiry date should also be recorded in the entry.

If a prescriber or drug service loses (or has stolen from them) a drug with abuse potential, they must immediately notify the Controlled Drugs Accountable Officer. The police should also be notified where theft has occurred.

12.4 Authority to prescribe and administer BPN injections

No specific authorisation is required to prescribe Buvidal® in the UK, other than to be a registered medical or non-medical prescriber. Healthcare professionals must have the necessary competencies and/or skills to prescribe and administer Buvidal®, as reflected in their area of expertise, training, appraisal and revalidation.

Appendix 1 Depot BPN studies

Study reference	Product	Setting	Author
NCT02672111 HS-14-499 (Braeburn)	Buvidal®	Community US/EU/AUS	Frost et al 2019

Aims: To assess long-term safety of subcutaneous buprenorphine depot (CAM2038) weekly and monthly regimens in adult outpatients with opioid use disorder.

Methods: This phase 3, open-label, multicentre, 48-week study (ClinicalTrials.gov NCT02672111) was conducted at 26 sites (US, UK, Hungary, Denmark, Sweden, Germany, and Australia). Participants were administered CAM2038 weekly (8, 16, 24, or 32mg) or CAM2038 monthly (64, 96, 128, or 160mg) with flexible dosing and individualised titration up or down utilising the multiple CAM2038 weekly and monthly dosing options. Safety variables, urine toxicology samples, and self-reported illicit opioid use were collected at each visit. 162/227 (71.4%) participants were administered a patient satisfaction survey.

Results: Between December 14, 2015, and April 12, 2017, 228 opioid-dependent participants enrolled, and 227 participants received CAM2038 (37 initiated directly onto CAM2038 and 190 converted from sublingual buprenorphine). 167/227 (73.6%) participants completed the treatment period. 143/227 (63.0%) participants reported at least 1 treatment emergent adverse event (TEAE), and 60/227 (26.4%) reported a drug-related TEAE. 46/227 (20.3%) participants reported injection site reactions, with most (45/46 [97.8%]) reported as mild to moderate. 128/227 (56.4%) of the TEAEs were mild or moderate in severity. Five participants (2.2%) discontinued study drug due to a TEAE, of which 2 cases (0.9%) were injection site related. No serious AEs were attributed to study drug. At end of study, the percentage of the composite outcome comprising illicit opioid-negative urine samples and self-reports was 63.0% (17/37) in new-to-treatment participants and 82.8% (111/190) for participants converted from sublingual buprenorphine. Participants reported high levels of satisfaction with CAM2038.

Conclusions: CAM2038 was well-tolerated and demonstrated a systemic safety profile consistent with the known profile of sublingual buprenorphine. Weekly and monthly CAM2038 was associated with high retention rates and low levels of continued illicit opioid use throughout the study[29].

Study reference	Product	Setting	Author
NCT02611752 HS-13-478 (Braeburn)	Buvidal®	US	Walsh et al 2017

Importance: Buprenorphine is an efficacious, widely used treatment for opioid use disorder (OUD). Daily oral transmucosal formulations can be associated with misuse, diversion, and nonadherence; these limitations may be obviated by a sustained release formulation.

Objective: To evaluate the ability of a novel, weekly, subcutaneous buprenorphine depot formulation, CAM2038, to block euphorigenic opioid effects and suppress opioid withdrawal in non–treatment-seeking individuals with OUD. Design, Setting and Participants: This multisite, double-blind, randomized within-patient study was conducted at 3 controlled inpatient research facilities. It involved 47 adults with DSM-V moderate-to-severe OUD. The study was conducted from October 12, 2015 (first patient enrolled), to April 21, 2016 (last patient visit).

Interventions: A total of five 3-day test sessions evaluated the response to hydromorphone (0, 6, and 18mg intramuscular in random order; 1 dose/session/day). After the first 3-day session (ie, qualification phase), participants were randomized to either CAM2038 weekly at 24mg (n = 22) or 32mg (n = 25); the assigned CAM2038 dose was given twice, 1 week apart (day 0 and 7). Four sets of sessions were conducted after randomization (days 1-3, 4-6, 8-10, and 11-13). Weekly CAM2038 doses were initiated directly from adults maintained on oral morphine.

Main Outcomes and Measures: The primary end point was maximum rating on the visual analog scale for drug liking. Secondary end points included other visual analog scale (eg, high and desire to use), opioid withdrawal scales, and physiological and pharmacokinetic outcomes

Results: A total of 46 of 47 randomized participants (mean [SD] age, 35.5 [9] years; 76% male [n = 35]) completed the study. Both weekly CAM2038 doses produced immediate and sustained blockade of hydromorphone effects (liking maximum effect, CAM2038, 24mg: effect size, 0.813; P < .001, and CAM2038, 32mg: effect size, 0.753; P < .001) and suppression of withdrawal (Clinical Opiate Withdrawal Scale, CAM2038, 24mg: effect size, 0.617; P < .001, and CAM2038, 32mg: effect size, 0.751; P < .001). CAM2038 produces a rapid initial rise of buprenorphine in plasma with maximum concentration around 24 hours, with an apparent half-life of 4 to 5 days and approximately 50% accumulation of trough concentration from first to second dose (trough concentration = 0.822 and 1.23 ng/mL for weeks 1 and 2, respectively, with 24mg; trough concentration = 0.993 and 1.47 ng/mL for weeks 1 and 2, respectively, with 32mg).

Conclusions and Relevance: CAM2038 weekly, 24 and 32mg, was safely tolerated and produced immediate and sustained opioid blockade and withdrawal suppression without any evidence of precipitating withdrawal upon depot initiation. The results support the use of this depot formulation for treatment initiation and stabilization of patients with OUD, with the further benefit of obviating the risk for misuse and diversion of daily buprenorphine while retaining its therapeutic benefits[10].

Study reference	Product	Setting	Author
EudraCT # 2008-006348-20 HS-07-307 (Camurus AB)	Buvidal®	Hamburg, Germany	Haasen et al 2017

Introduction: Sublingual buprenorphine is effective for opioid dependence treatment but associated with misuse, abuse, and diversion. The present Phase I/II study evaluated a novel buprenorphine subcutaneous depot formulation for once-weekly dosing (CAM2038 q1w) in patients receiving maintenance treatment for opioid use disorder with daily sublingual buprenorphine.

Methods: After discontinuation of buprenorphine for 48 h, patients received a single CAM2038 q1w dose based on their pre-study daily sublingual maintenance dose. CAM2038 q1w doses of 7.5, 15, 22.5, and 30mg were administered in a sequential dose-escalating design. The following assessments were performed: pharmacokinetics of buprenorphine and norbuprenorphine, pharmacodynamics (evaluated using the Subjective and Clinical Opiate Withdrawal Scales), and time to intake of rescue sublingual buprenorphine medication.

Results: Single doses of CAM2038 q1w indicated dose-proportional buprenorphine pharmacokinetics (Cmax and AUC0–7d), with time to Cmax ~20 h and an apparent terminal half-life of 3–5 days, supporting once-weekly dosing. On average, patients showed a rapid and extended decrease in opiate-withdrawal symptoms from baseline, with zero or very low SOWS and COWS values measured at least up to 7 days after dosing of CAM2038 q1w. The median time to first use of rescue buprenorphine was 10 days. No dose dependence was seen in the pharmacodynamics, attributable to the selection of CAM2038 q1w doses based on patients' pre-study maintenance doses. CAM2038 q1w was safe and generally well tolerated.

Study reference	Product	Setting	Author
HS-11-426 (Camurus AB) HS-13-487 (Camurus AB)	Buvidal®	UK	Liu et al 2018

CAM2038, FluidCrystal injection depot, is an extended release formulation of buprenorphine given subcutaneously every 1 week (Q1W) or every 4 weeks (Q4W). The purpose of this research was to predict the magnitude of drug- drug interaction (DDI) after coadministration of a strong CYP3A4 inducer or inhibitor using physiologically based pharmacokinetic (PBPK) modelling.

A PBPK model was developed for CAM2038 based on the previously published buprenorphine PBPK model after intravenous and sublingual administration and the PK profiles after subcutaneous administration of CAM2038 from 2 phase I clinical trials. The strong CYP3A4 inhibitor ketoconazole was predicted to increase the buprenorphine exposure by 35% for the Q1W formulation and 34% for Q4W formulation, respectively. Also, the strong CYP3A4 inducer rifampin was predicted to decrease the buprenorphine exposure by 26% for both the Q1W and Q4W formulations.

The results provided insight into the potential DDI effect for CAM2038 and suggested a lack of clinically meaningful DDI when CAM2038 is co-administered with CYP3A4 inhibitor or inducer. Therefore, no dose adjustment is required when CAM2038 is co-administered with CYP3A4 perpetrators [30].

Conclusions: Pharmacokinetics and pharmacodynamics of a novel buprenorphine subcutaneous depot formulation for once-weekly dosing was evaluated, suggesting utility in maintenance treatment of patients with opioid use disorder [31].

Study reference	Product	Setting	Author
NCT02651584 HS-11-421 (Braeburn	Buvidal®	Community US	Lofwall et al 2018

Objective: To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is non-inferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.

Design, Setting and Participants: This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.

Interventions: Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).

Main Outcomes and Measures: Primary end points tested for non-inferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 pre-specified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated non-inferiority.

Results: A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95%CI, −4.0% to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95%CI, −0.1%to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.

Conclusions and Relevance: Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages [10].

Study reference	Product	Setting	Author
ISRCTN24987553 HS-13-487 (Camurus AB)	Buvidal®	UK	Albayaty et al 2017

Introduction: CAM2038 q1w (once weekly) and q4w (once monthly) are investigational buprenorphine subcutaneous (SC) formulations based on FluidCrystal® injection depot technology. These two drug products are being developed for opioid dependence treatment, with a target for once-weekly and once-monthly SC dosing. The rationale for developing two products with different dosing frequencies is that treatment strategies/routines, and hence different treatment preferences, can vary between patients, different stages of opioid maintenance treatment, and countries. This study evaluated the pharmacokinetics and safety of buprenorphine and norbuprenorphine following administration of CAM2038 q1w or q4w versus active controls.

Methods: Healthy volunteers were randomized to five treatment groups. All received a single intravenous dose of buprenorphine 600 micrograms, followed post-washout by a single dose of CAM2038 q4w 96mg, a single dose of CAM2038 q4w 192mg, or sublingual buprenorphine 8, 16, or 24mg daily for 7 days, followed post-washout by a single dose of CAM2038 q4w 64 or 128mg or four repeated weekly doses of CAM2038 q1w 16mg. All subjects received daily naltrexone.

Results: Eighty-seven subjects were randomized. Median buprenorphine tmax after CAM2038 q4w was 4–10 h (24 h for CAM2038 q1w); mean terminal half-life was 19–25 days (5 days for CAM2038 q1w). CAM2038 q4w showed dose-proportional buprenorphine release, with similar exposure to repeat-dose CAM2038 q1w at comparable monthly dose level. Both CAM2038 formulations showed complete absolute bioavailability of buprenorphine and 5.7- to 7.7-fold greater buprenorphine bioavailability versus sublingual buprenorphine. CAM2038 q1w and q4w were well tolerated; subjects' acceptance was higher for CAM2038 than for sublingual buprenorphine 1 h post-dose.

Conclusions: The pharmacokinetic profiles of CAM2038 q1w and q4w versus sublingual buprenorphine support expected treatment efficacy with once-weekly and once-monthly dosing, respectively. CAM2038 formulations were safe and showed good local tolerability [32].

Appendix 2 Adverse reactions (from Buvidal SPC)

Adverse reactions listed by body system				
System Organ Class	Very common	Common	Uncommon	Not known
Infections and infestations		Infection Influenza Pharyngitis Rhinitis	Injection site cellulitis	
Blood and lymphatic system disorders		Lymphadenopathy		
Immune system disorders		Hypersensitivity		
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders	Insomnia	Anxiety Agitation Depression Hostility Nervousness Thinking abnormal Paranoia Medical dependence		Hallucinations Euphoric mood
Nervous system disorders	Headache	Somnolence Dizziness Migraine Paraesthesia Syncope Tremor Hypertonia Speech disorders		
Eye disorders		Lacrimal disorder Mydriasis Miosis		
Ear and labyrinth disorders			Vertigo	
Cardiac disorders		Palpitations		
Vascular disorders		Vasodilation Hypotension		
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea Yawning Asthma Bronchitis		
Gastrointestinal disorders	Nausea	Constipation Vomiting Abdominal pain		

		Flatulence Dyspepsia Dry mouth Diarrhoea Gastrointestinal disorder		
Hepatobiliary disorders			Alanine aminotransferase increased Aspartate aminotransferase increased Hepatic enzymes increased	
Skin and subcutaneous tissue disorders		Rash Pruritus Urticaria	Rash macular	Erythema
Musculoskeletal and connective tissue disorders		Arthralgia Back pain Myalgia Muscle spasms Neck pain Bone pain		
Renal and urinary disorders				Urinary retention
Reproductive system and breast disorders		Dysmenorrhoea		
General disorders and administration site conditions	Hyperhidrosis Drug withdrawal syndrome Pain	Injection site pain Injection site pruritus Injection site erythema Injection site swelling Injection site reaction Injection site induration Injection site mass Oedema peripheral Asthenia Malaise Pyrexia Chills Neonatal withdrawal syndrome Chest pain	Injection site inflammation Injection site bruising Injection site urticaria	
Investigations		Abnormal liver function tests		
Injury, poisoning and procedural complications			Procedural dizziness	

Appendix 3 Drug-drug interactions (DDIs)

Drug-drug interactions of potential clinical relevance with depot BPN

No interaction studies have been performed with Buvidal.

Buprenorphine should be used cautiously when co-administered with:

• benzodiazepines: This combination may result in death due to respiratory depression of central origin. Therefore, dosages must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines whilst taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as directed by their physician

• gabapentinoids: 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. Patients should be cautioned to use gabapentinoids (such as pregabalin and gabapentin) concurrently with this product only as directed by their physician

• alcoholic drinks or medicinal products containing alcohol as alcohol increases the sedative effect of buprenorphie

• other central nervous system depressants: Other opioid derivatives (e.g. methadone, analgesics and antitussives); certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, antipsychotics, clonidine and related substances. These combinations increase central nervous system depression. The reduced level of alertness can make driving and using machinery hazardous

• opioid analgesics: Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. The potential for overdose also exists with a full agonist, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining

• naltrexone and nalmefene: These are opioid antagonists that can block the pharmacological effects of buprenorphine. For opioid-dependent patients currently receiving buprenorphine 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 buprenorphine administration may be blocked by naltrexone.

• Buprenorphine is metabolised to norbuprenorphine primarily by CYP3A4. The effects on buprenorphine exposure in patients treated with Buvidal have not been studied. Interaction with co-administered inducers or inhibitors have been established in studies using transmucosal and transdermal buprenorphine. Buprenorphine is also metabolised to buprenorphine-3β-glucuronide by UGT1A1.

  • CYP3A4 inhibitors may inhibit the metabolism of buprenorphine resulting in increased C_{max} and AUC of buprenorphine and norbuprenorphine. Buvidal avoids first-pass effects and CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, or azole antifungals such as ketoconazole or itraconazole, or macrolide antibiotics) are expected to have less effects on buprenorphine metabolism when co-administered with Buvidal as compared to when co-administered with sublingual buprenorphine. When switching from sublingual buprenorphine to Buvidal, patients may need to be monitored to ensure plasma buprenorphine levels are adequate. Patients already on Buvidal who start treatment with CYP3A4 inhibitors should be treated with weekly Buvidal and be monitored for signs and symptoms of overtreatment. Conversely, if a patient who is concomitantly treated with Buvidal and a CYP3A4 inhibitor stops treatment with the CYP3A4 inhibitor, the patient should be monitored for symptoms of withdrawal.
  • CYP3A4 inducers may induce the metabolism of buprenorphine resulting in decreased buprenorphine levels. Buvidal avoids first-pass effects and CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are expected to have less effects on buprenorphine metabolism when co-administered with Buvidal as compared to when co-administered with sublingual buprenorphine. When switching from sublingual buprenorphine to Buvidal, patients may

need to be monitored to ensure plasma buprenorphine levels are adequate. Patients already on Buvidal who start treatment with CYP3A4 inducers should be treated with weekly Buvidal and be monitored for signs and symptoms of withdrawal. Conversely, if a patient who is concomitantly treated with Buvidal and a CYP3A4 inducer stops treatment with the CYP3A4 inducer, the patient should be monitored for symptoms of overtreatment.

- UGT1A1 inhibitors may affect the systemic exposure of buprenorphine.

- monoamine oxidase inhibitors (MAOI): Possible exacerbation of the opioids effects, based on experience with morphine.

Appendix 4 Special precautions for handling

• Administration should be made into the subcutaneous tissue

• Intravascular, intramuscular and intradermal administration must be avoided.

- Choose the injection site. Injections should be rotated between sites in the buttock, thigh, abdomen, or upper arm (see Figure 3) with a minimum of 8 weeks before re-injecting a previously used injection site. Injections on the waistline or within 5 cm of the navel should be avoided.

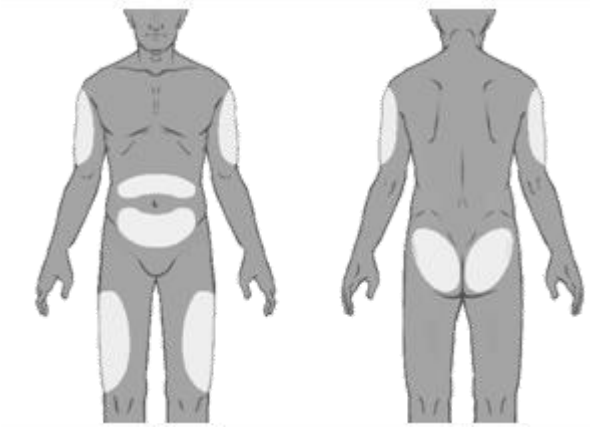

Figure 3:

- Put on gloves and clean the injection site with a circular motion using an alcohol wipe (not provided in the pack). Do not touch the cleaned area again before injecting.

- While holding the safety syringe by the syringe guard body as shown (see Figure 4), carefully pull the needle shield straight off. Immediately dispose of the needle shield (never try to recap the needle). A drop of liquid may be seen at the end of the needle. This is normal.

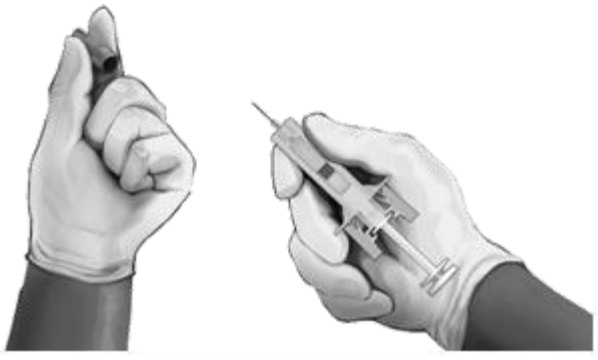

Figure 4:

- Pinch the skin at the injection site between the thumb and finger as shown (see Figure 5).

- Hold the safety syringe as shown and smoothly insert the needle at an angle of approximately 90° (see Figure 5). Push the needle all the way in.

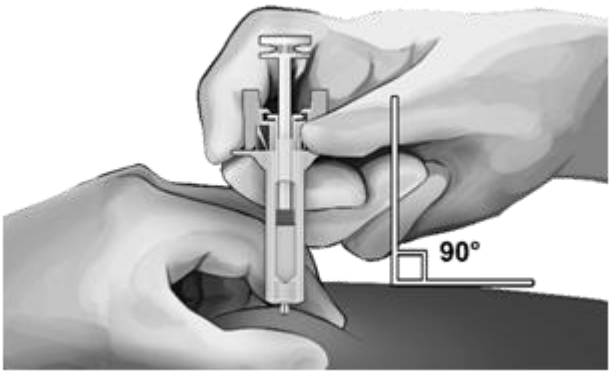

Figure 5:

- While holding the syringe as shown (see Figure 6), slowly depress the plunger until the plunger head latches between the syringe guard wings and all the solution is injected.

Figure 6:

- Gently pull the needle out of the skin. It is recommended that the plunger is kept fully depressed while the needle is carefully lifted straight out from the injection site (see Figure 7).

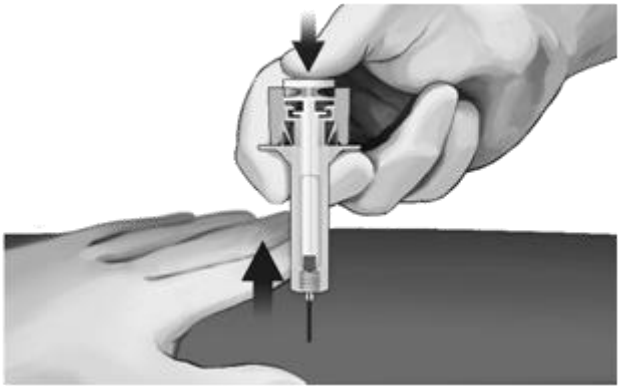

Figure 7:

- As soon as the needle has been completely removed from the skin, slowly take the thumb off the plunger and allow the syringe guard to automatically cover the exposed needle (see Figure 8). There may be a small amount of blood at the injection site, if required wipe with a cotton ball or gauze.

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