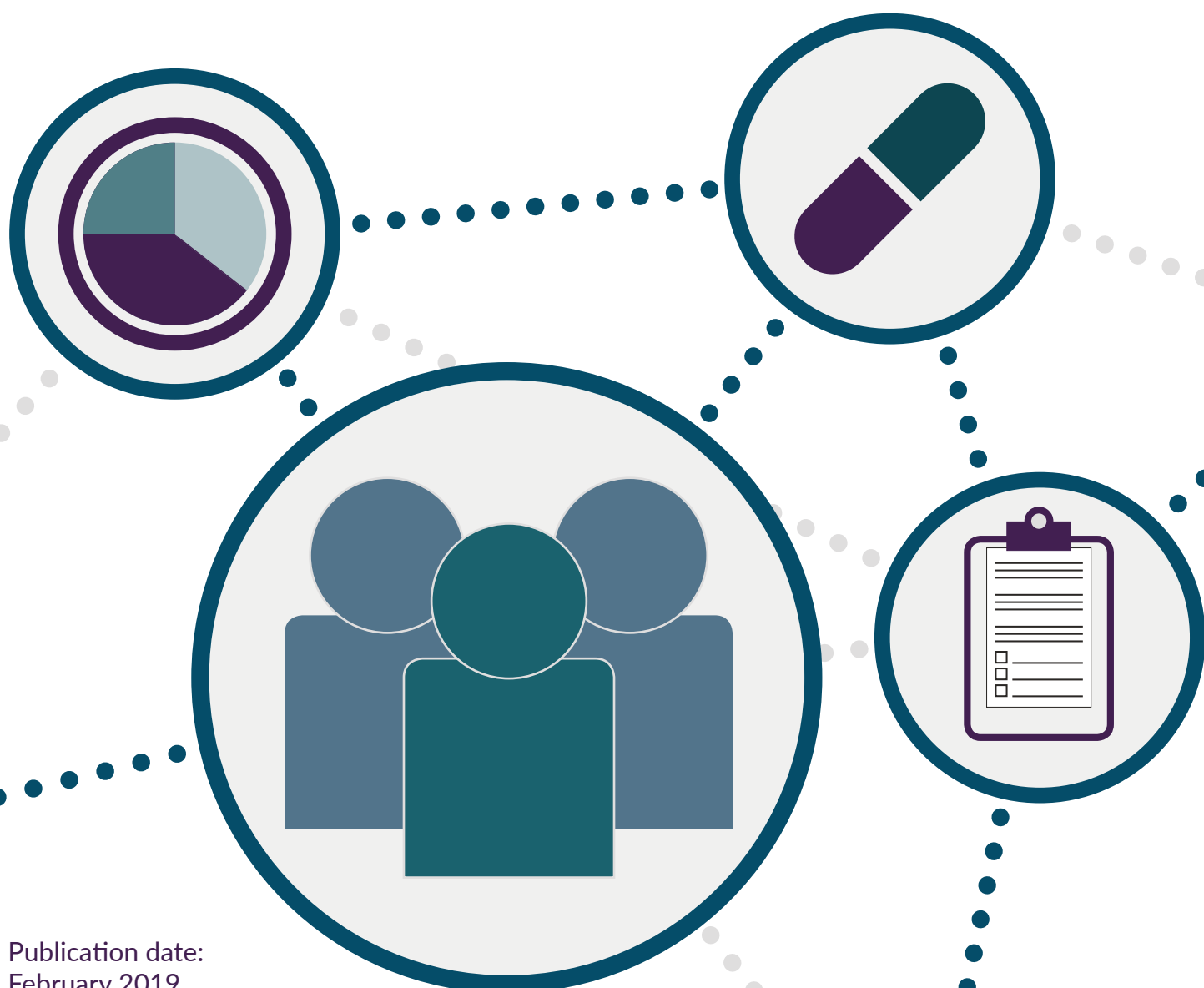


Opioid dependence: buprenorphine prolonged- release injection (Buvidal)



This evidence review sets out the best available evidence on buprenorphine prolonged-release injection (Buvidal) for treating opioid dependence. It should be read in conjunction with the evidence summary, which gives the key messages.

Commissioned by Public Health England.

Disclaimer

The content of this evidence review was up-to-date in February 2019. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

The UK has relatively high rates of heroin and crack cocaine misusers compared with many other western countries. However, the proportion of these drug misusers in treatment is also very high compared with many other countries. Most adult drug misusers in treatment in the UK report opiates (primarily heroin) as their main problem drugs ([UK guidelines on clinical management of drug misuse and dependence, 2017](#)).

Methadone and buprenorphine are both effective medicines for maintenance treatment of opioid dependence, particularly when taken within the optimal dose range. The NICE technology appraisal on [methadone and buprenorphine for the management of opioid dependence](#) recommends that either of these drugs (as oral formulations), using flexible dosing regimens, are options for maintenance therapy in the management of opioid dependence.

Supervised consumption should be available to all people to support induction on to opioid substitution therapy, and provided for a length of time appropriate to their individual needs and risks. Those on supervised consumption will often still have take-home medication on Sundays and some bank holidays (UK guidelines on clinical management of drug misuse and dependence, 2017). Risks of providing take-home medication may include accidental ingestion of opioid substitution medicines by children and others, and risks of diversion.

In some settings, such as custodial environments, supervised consumption of opioid substitution therapy is mandatory for the time the person is resident in the secure environment.

Product overview

Mode of action

Buvidal is a prolonged-release injection of buprenorphine used in opioid dependence. Buprenorphine is an opioid partial agonist/antagonist which binds to the mu and kappa opioid receptors in the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the mu opioid receptors which, over time, might minimise the need for illicit opioids for people with opioid dependence ([summary of product characteristics](#)).

Regulatory status

Buprenorphine prolonged-release injection (Buvidal) has a marketing authorisation for treating opioid dependence within a framework of medical, social and psychological treatment in adults and young people aged 16 years and over (summary of product characteristics).

Dosing information

Buprenorphine prolonged-release injection is available as a weekly injection in 8 mg, 16 mg, 24 mg and 32 mg strengths and a monthly injection in 64 mg, 96 mg and 128 mg strengths.

A healthcare professional should give buprenorphine prolonged-release injection subcutaneously. It must not be administered intravenously, intramuscularly or intradermally. Take-home use or self-administration should not be allowed.

To avoid precipitating symptoms of withdrawal, treatment should be started when there are clear signs of mild to moderate opioid withdrawal. For people using heroin or short-acting opioids, the first dose should be given at least 6 hours after the last use of opioids. For people receiving methadone, the methadone dose should be reduced to a maximum of 30 mg per day before starting treatment, which should begin at least 24 hours after the last methadone dose.

People who have not had buprenorphine before should have 4 mg of sublingual buprenorphine with observation for 1 hour, before receiving buprenorphine prolonged-release injection for the first time. This is to confirm that buprenorphine can be tolerated.

For people not already receiving buprenorphine, the recommended starting dose is 16 mg of the weekly formulation of buprenorphine prolonged-release injection, with 1 or 2 additional 8-mg doses given at least 1 day apart to reach a target dose of 24 mg or 32 mg during the first week. The recommended dose in the second week is the total dose given during the first week given in a single weekly injection. Monthly injections can be started once a person is stable on weekly injections, preferably after 4 weeks or more.

People already receiving sublingual buprenorphine can be switched directly on to weekly or monthly buprenorphine injections, starting the day after the last sublingual dose, according to the dose conversion recommendations provided in the summary of product characteristics.

The dose of buprenorphine prolonged-release injection can be increased or decreased, with switching between weekly and monthly preparations according to individual needs and clinical judgement. A maximum of 1 additional 8 mg dose can be given between regular weekly or monthly doses if needed. The maximum dose per week is 32 mg with 1 additional 8 mg dose. For people on monthly injections, the maximum dose is 128 mg per month, with 1 additional 8 mg dose (summary of product characteristics).

The prolonged-release characteristics of the injection should be taken into account when treatment is stopped. Sublingual buprenorphine should not be given until 1 week after the last weekly dose or 1 month after the last monthly dose (summary of product characteristics).

Effectiveness

This evidence review discusses the best available evidence for buprenorphine prolonged-release injection (Buvidal), which is 1 phase 3, [double-blind](#), double-dummy, 24-week [randomised controlled trial](#) (RCT; [Lofwall et al. 2018](#)). An additional open-label, 48-week safety study (with secondary efficacy outcomes) has completed but results have not been published yet ([NCT02672111](#)). The efficacy of buprenorphine prolonged-release injection is supported by secondary outcomes from this study, reported in the [European Public Assessment Report \(EPAR\) for Buvidal](#). Safety outcomes from this study are briefly discussed in the [safety section](#) using information from the [EPAR for Buvidal](#).

The RCT by Lofwall et al. (2018) included 428 adults (mean age 38.4 years, 61% male) diagnosed with, and seeking treatment for, moderate to severe opioid use disorder. Around 70% of people reported that their primary opioid of use at screening was heroin. The RCT compared treatment with weekly then monthly buprenorphine prolonged-release injection, with daily sublingual buprenorphine-naloxone tablets. The 2 primary outcomes were the mean percentage of opioid-negative urine samples during weeks 1 to 24, and the [responder rate](#) (defined as no evidence of illicit opioid use at pre-specified time points within the study).

A summary of the included study can be found in [Appendix A: Summary of included study](#). An overview of the results for clinical effectiveness can be found in [Appendix B: Results tables](#). [Appendix E: Studies excluded and not-prioritised](#) gives details of studies identified in the literature search that were subsequently excluded or not prioritised.

Opioid-negative urine samples

In Lofwall et al. (2018), buprenorphine prolonged-release injection was non-inferior to sublingual buprenorphine-naloxone for the mean percentage of opioid-negative urine samples during weeks 1 to 24 (primary outcome; 35.1% for buprenorphine prolonged-release injection compared with 28.4% for sublingual buprenorphine-naloxone, treatment difference 6.7%, 95% [confidence interval](#) [CI] -0.1% to 13.6%, $p < 0.001$). Non-inferiority was shown because the lower limit of the 95% CI for the treatment difference was within the pre-specified margin of 11%. Analysis of this primary outcome was completed in the [intention-to-treat](#) population. Sensitivity analyses for this endpoint (where missing data were not imputed, and where negative opioid urine tests were supported by self-report of no illicit opioid use) were consistent with the main findings.

Superiority testing could only be performed if non-inferiority was demonstrated for the primary outcomes. The mean proportion of urine samples with no evidence of illicit opioid use (affirmed by self-report of no illicit opioid use) during weeks 4 to 24, evaluated by a cumulative distribution function (CDF), was a secondary outcome testing superiority. Buprenorphine prolonged-release injection was superior to sublingual buprenorphine-naloxone (CDF of mean proportion of opioid-negative urine samples affirmed by self-report of no illicit opioid use 35.1% for buprenorphine prolonged-release injection compared with

26.7% for sublingual buprenorphine-naloxone. Median CDF was 27.6% for buprenorphine prolonged-release injection and 0.0% for sublingual buprenorphine-naloxone; $p = 0.004$).

Responder rate

For the other primary outcome in the trial, buprenorphine prolonged-release injection was non-inferior to sublingual buprenorphine-naloxone for the percentage of responders ([responder rate](#); 17.4% for buprenorphine prolonged-release injection compared with 14.4% for sublingual buprenorphine-naloxone, treatment difference 3.0%, 95% CI -4.0% to 9.9% , $p < 0.001$). Non-inferiority was shown because the lower limit of the 95% CI for the treatment difference was within the pre-specified margin of 10%. Analysis of this primary outcome was completed in the intention-to-treat population. Sensitivity analyses were not reported for this outcome.

Superiority of buprenorphine prolonged-release injection for the percentage of responders was tested as a secondary outcome. Buprenorphine prolonged-release injection was not superior to sublingual buprenorphine-naloxone for this outcome. No figures were reported.

Study retention

Study retention was analysed as a secondary outcome. At week 24, the proportion of people still in the study was 69.0% for the buprenorphine prolonged-release injection group, and 72.6% for the sublingual buprenorphine-naloxone group (treatment difference -3.5% , 95% CI -12.2% to 5.1% , $p = 0.009$). Buprenorphine prolonged-release injection was non-inferior to sublingual buprenorphine-naloxone because the lower limit of the 95% CI for the treatment difference was within the pre-specified margin of 15%. Similar results were reported at week 12 and week 28, and buprenorphine prolonged-release injection was non-inferior to sublingual buprenorphine-naloxone at both time points.

Opioid craving and withdrawal symptoms

Opioid craving (measured using [desire- and need-to-use opioid visual analogue scales \[VAS\]](#)) and withdrawal symptoms (measured using [clinical opiate withdrawal scale](#) and the [subjective opiate withdrawal scale](#)) were investigated as exploratory outcomes. Lofwall et al. (2018) report that opioid craving measured on the need-to-use opioid VAS, and withdrawal symptoms measured on the clinical opiate withdrawal scale were suppressed immediately in both groups from day 1 of the trial and throughout the study with no significant between group differences. The results for these outcomes were reported graphically in the study. Data on opioid withdrawal symptoms measured using the subjective opiate withdrawal scale, and opioid craving measured using the desire-to-use opioid scale were not reported in the study. Some additional data for these outcomes are available in the EPAR for Buvidal.

Additional buprenorphine doses

In weeks 12 to 24 of the RCT, 6.6% of people in the buprenorphine prolonged-release injection group and 7.9% of people in the sublingual buprenorphine-naloxone group received

additional doses of 8 mg of the weekly formulation of buprenorphine prolonged-release injection. The total number of additional doses was 23 for the buprenorphine prolonged-release injection group and 28 for the sublingual buprenorphine-naloxone group. No statistical analyses were reported.

Psychosocial counselling

Attendance for counselling during scheduled weekly and monthly study visits was high in both groups (mean attendance: 96.1% in the buprenorphine prolonged-release injection group compared with 94.1% in the sublingual buprenorphine-naloxone group). A total of 15 people in the buprenorphine prolonged-release injection and 14 people in the sublingual buprenorphine-naloxone group had additional counselling sessions (1 to 3 extra sessions per person).

Safety

An overview of the study results for safety and tolerability can be found in [Appendix B: Results tables](#).

In the RCT by [Lofwall et al. \(2018\)](#), the most common adverse events in the buprenorphine prolonged-release injection group were injection site pain (8.9%), headache (7.5%), constipation (7.5%), nausea (7.0%), injection site pruritus (6.1%) and injection site erythema (5.6%). These were also the most common adverse events in the sublingual buprenorphine-naloxone (placebo injection) group with similar proportions of participants experiencing these. All injection site adverse events were mild to moderate in intensity. Insomnia was reported by slightly more people in the buprenorphine prolonged-release injection group compared with the sublingual buprenorphine-naloxone group (5.6% compared with 2.8%). No statistical analyses were reported.

One participant in the buprenorphine prolonged-release injection group experienced a serious adverse event (vomiting of moderate intensity) that was considered related to the study treatment. Six people were hospitalised for infections that may have been related to illicit injection-drug use (such as osteomyelitis, cellulitis and sepsis); all but 1 were in the sublingual buprenorphine-naloxone group. Five non-fatal overdoses of non-study drugs (4 accidental and 1 intentional) were reported, which were all in the sublingual buprenorphine-naloxone group. Ten people discontinued study treatment because of an adverse event; 4 because of injection site reaction (3 in the buprenorphine prolonged-release injection group and 1 in the sublingual buprenorphine-naloxone [placebo injection] group). The remaining 6 discontinuations were because of non-cardiac chest pain, sedation, nausea and vomiting, nausea and self-induced vomiting with subsequent oesophageal rupture, all of which occurred in the buprenorphine prolonged-release injection group; and sepsis and drug withdrawal after being jailed without access to study medication, which occurred in the sublingual buprenorphine-naloxone group.

In the open-label, 48-week safety study ([NCT02672111](#)), the most common adverse events reported in 156 people who completed study visits for week 48 and received their last injection were injection site pain (14.7%), injection site swelling (12.8%), nasopharyngitis (10.3%), nausea (9.6%), injection site erythema (9.0%), headache (7.7%), vomiting (7.7%), urinary tract infection (5.8%), diarrhoea (5.1%), migraine (5.1%), pain in extremity (5.1%) and hypertension (5.1%; [European Public Assessment Report \[EPAR\] for Buvidal](#)).

The EPAR states that safety of buprenorphine prolonged-release injection is similar to oral buprenorphine with the exception of injection site reactions, which are frequent. There are no safety data for people younger than 18 years or older than 66 years. Buprenorphine prolonged-release injection is indicated for maintenance treatment in opioid dependence with indefinite treatment length. Long-term safety data are limited to the 48-week safety study discussed above.

The [summary of product characteristics](#) states that the most commonly reported adverse events (occurring in more than 1 in 10 people) for buprenorphine (including buprenorphine prolonged-release injection) are headache, nausea, hyperhidrosis, insomnia, drug withdrawal and pain.

Deaths from respiratory depression have been reported in people treated with buprenorphine particularly when used in combination with benzodiazepines. Deaths have also been reported when buprenorphine is used in combination with other depressants (such as alcohol), pregabalin, gabapentin or other opioids. The summary of product characteristics warns that if buprenorphine prolonged-release injection is used with benzodiazepines, or pregabalin or gabapentin, dosages should be carefully monitored and the combinations avoided if there is a risk of misuse. People should be counselled about the dangers of taking non-prescribed benzodiazepines while receiving the prolonged-release injection.

Once administered, the prolonged-release injection dose cannot be removed (Camurus: personal communication 2018). In the case of overdose, the long duration of action of buprenorphine along with the prolonged-release properties of the subcutaneous injection should be taken into account when determining length of treatment needed to reverse the effects of overdose. An opioid antagonist (such as naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioids. Buprenorphine subcutaneous injection is contraindicated in people with severe respiratory insufficiency, severe hepatic impairment or people with acute alcoholism or delirium tremens. Liver function should be monitored regularly while receiving treatment with buprenorphine prolonged-release injection (summary of product characteristics).

Person-related factors

Buprenorphine prolonged-release injection may offer benefits to some people because it removes the need for regular attendance (commonly daily) at primary care for dispensing or supervised consumption of opioid substitution medicine. This may offer advantages for

people who have difficulties adhering to daily supervised opioid substitution medication, such as for people who are working or who are in education.

Some people may not want to use an injectable form of opioid substitution therapy and may prefer an oral therapy. Injection site reactions can happen after the injection is given and around 17% of people in the Lofwall et al. (2018) trial experienced these ([summary of product characteristics](#)).

Buprenorphine prolonged-release injection is recommended to be used up to a weekly maximum dose of 32 mg or monthly maximum dose of 128 mg, which is approximately equivalent to 18 mg to 24 mg daily of sublingual buprenorphine. Therefore it may not be suitable for people with opioid substitution requirements that are greater than this. A maximum of 1 additional 8 mg dose can be given between regular weekly or monthly doses if needed, based on an individual person's temporary needs.

If people have acute pain that needs treating while receiving buprenorphine prolonged-release injection, a combination of opioids with high mu-opioid receptor affinity (for example fentanyl), non-opioid analgesics and regional anaesthesia might be needed. Higher doses of short-acting opioid pain medicines may be needed (summary of product characteristics).

Evidence strengths and limitations

The study by [Lofwall et al. \(2018\)](#) was a relatively large (n=428), well designed, double-blind, double-dummy trial. The [European Public Assessment Report for Buvidal](#) states that the chosen comparator (buprenorphine-naloxone sublingual tablets) was appropriate because naloxone does not affect the pharmacodynamic properties of buprenorphine and is added to prevent misuse. However, this combination tablet is not commonly prescribed for treating opioid dependence in the UK. The mean dosages of sublingual buprenorphine-naloxone taken in the trial (18.5 mg/day in the first 12 weeks and 19.6 mg/day in the second 12 weeks) were within the therapeutic dose range for treating opioid dependence. The mean dosages of the prolonged-release injection were similar in equivalence (approximately equivalent to sublingual buprenorphine 18.6 mg/day in the first 12 weeks and 19.1 mg/day in the second 12 weeks).

The trial was completed in US healthcare settings and only 1 of the study sites was primary care based. This may limit the applicability to UK practice. However the most common opioid misused by around 70% of participants at baseline was heroin which reflects the UK population where heroin is the main problem drug of most adult drug misusers.

The primary outcomes of Lofwall et al. (2018) appeared appropriate (and were required by regulatory authorities in Europe and USA). However, they were disease-orientated rather than patient-orientated outcomes; important outcomes for patients such as craving and withdrawal scores were only investigated as exploratory outcomes.

As discussed in the [UK guidelines on the clinical management of drug misuse and dependence](#), precipitated withdrawal can occur when buprenorphine is first administered to an opiate-dependent person with circulating opioid agonist drugs present. Precipitated withdrawal signs and symptoms were not reported by Lofwall et al. (2018). However, the [summary of product characteristics](#) provides information on how to avoid precipitating symptoms of withdrawal. See the [dosing information](#) section for more information.

Around 70% of people in the trial completed 24 weeks of treatment, representing a relatively high treatment retention rate. However, participants received expenses to attend study visits with average payments of \$50 per visit. This may have improved study retention rates and may not provide an accurate estimate of treatment retention rates in a real-world setting where people are not incentivised to attend follow-up visits. Participants received addiction counselling at scheduled weekly and monthly study visits and around 95% of people in each group attended scheduled sessions.

In UK practice, people starting maintenance treatment for opioid dependence would usually have daily supervised consumption of opioid substitution medication, principally buprenorphine and methadone. Supervision might be relaxed over time depending on individual circumstances, or if buprenorphine-naloxone is used because of its lower abuse potential. However, as recommended in the UK guidelines on clinical management of drug misuse and dependence (2017), no more than 1-week of take-home doses should be supplied in a single instalment. During phase 1 of the Lofwall et al. (2018) trial (first 12 weeks), participants received a 7-day supply of take-home buprenorphine-naloxone (the comparator treatment) or placebo tablets. During phase 2 (last 12 weeks), this increased to a 4-week supply. This means the trial did not mirror UK practice. Adherence to sublingual buprenorphine-naloxone was not assessed in Lofwall et al. (2018), therefore it is not possible to say if people in the sublingual buprenorphine-naloxone group adhered to their treatment.

An overview of the quality assessment of each included study can be found in [Appendix C: Quality assessment of included studies](#).

Resource impact

Buprenorphine is available as a prolonged-release injection in weekly strengths of 8 mg, 16 mg, 24 mg, and 32 mg; and monthly strengths of 64 mg, 96 mg and 128 mg. The cost for a 30-day supply, irrespective of the strength prescribed is £239.70.

The drug acquisition cost of buprenorphine prolonged-release injection compared with other medicines for opioid dependence can be seen in the table below.

Medicine	Usual dose ^a	30-day cost excluding VAT ^b
Buprenorphine prolonged-release injection	8–32 mg weekly 64–128 mg monthly	£239.70 ^c

Medicine	Usual dose ^a	30-day cost excluding VAT ^b
Buprenorphine sublingual tablets sugar free	12–24 mg daily	£139.41 to £246.73 ^d
Buprenorphine-naloxone sublingual tablets sugar free	12–24 mg daily	£137.44 to £247.37 ^d
Buprenorphine oral lyophilisate (Espranor)	8–18 mg daily	£81.64 to £190.50 ^d
Methadone oral solution 1 mg/ml sugar free	60–120 mg daily	£14.76 to £29.52 ^d
Methadone oral solution 1 mg/ml	60–120 mg daily	£14.94 to £29.88 ^d

^a Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the [BNF](#) or relevant [summaries of product characteristics](#), or based on specialist opinion.

^b Costs shown are for the drug acquisition cost only and do not include additional costs associated with dispensing, supervised consumption or administration of injections where these are necessary.

^c Buprenorphine prolonged-release injections will be priced at an equivalent cost of £7.99 per day irrespective of strength (Camurus: personal communication 2018).

^d Costs based on [Drug Tariff](#), February 2019; excluding VAT.

Likely place in therapy

One of the main advantages of buprenorphine prolonged-release injection is that it is administered as a weekly or monthly injection by a healthcare professional and does not need daily supervised use. This may offer advantages for some people who have difficulties adhering to supervised daily opioid substitution medication, such as for people who are working or who are in education. Additionally some people may dislike taking daily medication and may prefer a weekly or monthly treatment.

For most people being newly prescribed oral methadone or sublingual buprenorphine for opioid dependence, daily doses should be taken under the direct supervision of a professional for a period of time to allow monitoring of progress and ongoing risk assessment. In secure environments, all schedule 2, 3 and 4 controlled drugs (including buprenorphine) should be supplied under supervision unless in exceptional circumstances on an individual case basis (Royal Pharmaceutical Society [professional standards for optimising medicines for people in secure environments](#)). To protect patient and community safety, the [UK guidelines on clinical management of drug misuse and dependence \(2017\)](#) recommend that take-home doses should not normally be prescribed where:

- the person has not reached a stable dose
- the person shows a continued and unstable pattern of drug misuse, including a significant excessive level of alcohol intake, the use of illicit drugs and/or misuse of benzodiazepines or other tranquillisers
- the person has a significant, unstable psychiatric illness or is threatening self-harm

- there is continuing concern that the prescribed medicine is being, or may be, diverted or used inappropriately
- there are concerns about the safety of medicines stored in the home and possible risk to children.

In situations where there is risk of diversion or where there are concerns about the safety of medicines stored in the home, buprenorphine prolonged-release injection may be a suitable option because it eliminates these risks.

Issues with using sublingual buprenorphine in a prison setting include that it can be misused and diverted, and it takes greater time to supervise its consumption sublingually compared with oral methadone. The [UK guidelines on clinical management of drug misuse and dependence \(2017\)](#) discuss that there are some common clinical scenarios specific to the prison environment that all clinical staff need to be prepared to manage such as adapting community formularies to maximise safety (for example greater first-line use of methadone over buprenorphine). The guidelines recommend that in a prison setting, buprenorphine could be considered in:

- people who are currently prescribed buprenorphine as part of a community programme and for whom release is imminent
- mild cases of dependence in opioid users, for example, in some younger non-injecting heroin users
- clinical exceptions agreed in partnership with the clinician and the person.

There is no risk of diversion with buprenorphine prolonged-release injection and it does not need daily supervised administration, therefore it may have a place in custodial settings where the risk of diversion and time needed for supervised consumption currently leads to challenges in supplying supervised medicines safely.

In [Lofwall et al. \(2018\)](#) buprenorphine prolonged-release injection was compared with sublingual buprenorphine-naloxone, and most people (around 70%) reported that their primary opioid of use at screening was heroin. Therefore it is not possible to say how the efficacy and safety of buprenorphine prolonged-release injection compares with methadone, and the results may be less applicable to treating opioid dependence to substances other than heroin.

Once administered, the prolonged-release injection dose cannot be removed and, in the case of overdose, the long duration of action of buprenorphine along with the prolonged-release properties of the subcutaneous injection needs to be considered.

The drug acquisition cost of buprenorphine prolonged-release injection is higher than some commonly used treatments for maintenance treatment of opioid dependence in the UK such as methadone oral solution and some formulations and dosages of buprenorphine.

Additional costs of using buprenorphine prolonged-release injection include healthcare professional time and appropriate facilities to administer the injections. The increased drug acquisition cost compared with some treatments for opioid dependence, and additional administration costs of buprenorphine prolonged-release injection, might be partially offset against savings through removal of the need for dispensing and supervised consumption of medication.

Other formulations of long-acting buprenorphine for opioid dependence are in development but at the time of development of this evidence review (January 2019) none were available in the UK.

Development of the evidence review

Process

The [evidence summary: process guide](#) (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers and declarations of interest

Name, job title/organisations	DOI
Nigel Barnes, Chief Pharmacist, Birmingham & Solihull Mental Health Foundation Trust	No interests to declare.
Dr Owen Bowden-Jones, Consultant Psychiatrist, Central North West London NHS Foundation Trust, Chair, Advisory Council on the Misuse of Drugs (ACMD), National Clinical Adviser, Alcohol, Drugs and Tobacco Division, Public Health England	Clinical adviser, Public Health England. Discuss wide range of policy positions relating to drug policy (since 2015) Chair, ACMD. Provide advice to Government on evidence base relating to drug harms (since 2017) Honorary senior lecturer, Imperial College London. Research activities do not directly relate to opioid/opiate misuse, but occasionally asked to review articles relating to opioid substitution treatment (since 2003).
Denise Farmer, Pharmaceutical Adviser for Health and Justice, NHS England	No interests to declare.
Roz Gittins, Chief Pharmacist, Addaction	Writer for Indivior Respiratory Guidelines (August 2018 – ongoing) GPhC Statutory Committee Pharmacist member (June 2018 – ongoing) NICE Scholar (2018 – ongoing) Director of Pharmacy, Addaction (2017 – ongoing) CMHP credentialed and Council member (Registrar, previously Assistant Registrar), Trustee and Director (2016 – ongoing)

Name, job title/organisations	DOI
	<p>Editorial Board – Clinical Pharmacist (2017 – ongoing)</p> <p>RCGP accredited trainer for substance misuse and alcohol certificates (2014 – ongoing)</p> <p>Contributor - CPPE training/development tools (2016 – 2017)</p> <p>Pharmacist Topic Expert-NICE Alcohol guidelines update committee (2016 – 2017)</p>
Helen Marlow; Lead Primary Care Pharmacist, Surrey Downs Clinical Commissioning Group	External lecturer for Kings College London since 2003. Brother has worked for Roche Products since 1990.
Giles Owen, Deputy Director and Head of Prescribing & Medicines Management, NHS Corby Clinical Commissioning Group and NHS Nene Clinical Commissioning Group	No interests to declare.
Graham Parsons, Chief Pharmacist, Turning Point	<p>Payment for speaking at Pharmacy Show by Martindale (November 2017)</p> <p>International Conference attendance funded by Indivior (May 2018)</p> <p>IOTOD Conference (Madrid) 2018: received funding for accommodation and conference fees from Indivior</p> <p>Presented at RCGP/SMMGP Conference 2016, 2017 and 2018: accommodation and conference fees paid for as an external speaker (conferences jointly sponsored by a number of pharmaceutical companies and hosted by the RCGP and SMMGP)</p> <p>National Substance Misuse NMP Forum 2014-2018: member of the steering group from 2014 to October 2018 (a number of pharmaceutical companies sponsor annual local regional meetings (Camurus provided some joint funding with Martindale in 2018, no direct payment received)</p> <p>Guidelines on OST and COPD management (2018): currently writing a chapter for a guideline on this topic (guidance is supported by Indivior, but no payment for authorship - ongoing).</p>
Jon Vinson, Lead Medicines Management Pharmacist, NHS North Derbyshire Clinical Commissioning Group	<p>Shareholder in Wicker Pharmacy Sheffield (a community pharmacy) (1992 – ongoing).</p> <p>Lead Specialist Clinical Polices – Derbyshire Clinical Commissioning Groups (May 2018 – ongoing).</p>
Michael Wilcock, Head of Prescribing Support Unit, Pharmacy Department, Royal Cornwall Hospitals NHS Trust	On editorial board of Drug & Therapeutics Bulletin (2014 – ongoing).

Terms used in this evidence review

Responder rate

A responder was defined as having no evidence of illicit opioid use (urine test result and self-report of drug use both negative for illicit opioids) in phase 1 of the trial at week 12 and for at least 2 of 3 assessments at weeks 9 to 11, and in phase 2 of the trial for at least 5 of 6 assessments from weeks 12 to 24 including month 6 (weeks 21 to 24).

Clinical opiate withdrawal scale

The clinical opiate withdrawal scale has a score range of 0 indicating no withdrawal to 48 indicating severe withdrawal ([Lofwall et al. 2018](#)).

Subjective opiate withdrawal scale

The subjective opiate withdrawal scale has a score range of 0 indicating no withdrawal to 64 indicating severe withdrawal (Lofwall et al. 2018).

Desire- and need-to-use opioid visual analogue scales (VAS)

The desire- and need-to-use opioid visual analogue scales have a score range of 0 indicating no need or desire to use to 100 indicating maximum need or desire to use since last visit (Lofwall et al. 2018).

Appendices

Appendix A: Summary of included study

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
Lofwall et al. (2018) ¹ RCT 35 sites in the US ^a	n=428 (participants received treatment for 24 weeks and were followed up for a further 4 weeks)	Adults aged 18 to 65 years diagnosed with, and seeking treatment for, moderate to severe opioid use disorder ^b	Buprenorphine prolonged-release injection weekly for 12 weeks (mean dosage 26.6 mg/week [equivalent to approximately 18.6 mg/day sublingual buprenorphine]), and then monthly for 12 weeks (mean dosage 108.4 mg/month [equivalent to approximately 19.1 mg/day sublingual buprenorphine]), plus daily sublingual placebo tablets throughout all phases (n=213) ^c	Daily sublingual buprenorphine-naloxone (mean buprenorphine dosage 18.5 mg/day in the first 12 weeks and 19.6 mg/day in last 12 weeks), plus matched subcutaneous placebo injections (n=215) ^d	Mean percentage of urine samples negative for illicit opioids for weeks 1 to 24 Responder rate ^e	Participants received expenses to attend study visits 1 to 24 Participants received up to a 4-week supply of take-home buprenorphine-naloxone Adherence to sublingual buprenorphine-naloxone was not assessed

^a Only 1 of the included centres was primary care based.

^b Mean age of participants was 38.4 years, 61% of participants were male. Around 70% of people reported that their primary opioid of use at screening was heroin. A total of 23% of people in the sublingual buprenorphine-naloxone group and 30% of people in the buprenorphine prolonged-release injection group tested positive for fentanyl.

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
<p>^c The dosage of buprenorphine prolonged-release injection was titrated to a target dosage of 24 mg weekly with matched sublingual placebo during week 1. Dosages thereafter were flexible according to patient needs and clinical judgement. During the first 12 weeks (phase 1), visits were weekly; participants received weekly buprenorphine prolonged-release injections and a 7-day take-home supply of sublingual placebo. During the second 12 weeks (phase 2) visits were monthly; participants received monthly buprenorphine prolonged-release injections and a 4-week supply of take-home sublingual placebo. During phase 2, 1 additional 8 mg dose per month of the weekly formulation of buprenorphine prolonged-release injection was allowed. Addiction counselling was provided at each weekly and monthly visit, and additional counselling visits were accommodated as needed.</p> <p>^d The dosage of sublingual buprenorphine-naloxone was titrated to a target dosage of 16 mg/day with matched placebo injections during week 1. Dosages thereafter were flexible according to patient needs and clinical judgement. During the first 12 weeks (phase 1), visits were weekly; participants received weekly subcutaneous placebo injections and 7-days take-home sublingual buprenorphine-naloxone. During the second 12 weeks (phase 2) visits were monthly; participants received monthly subcutaneous placebo injections and a 4-week supply of take-home sublingual buprenorphine-naloxone. During phase 2, 1 additional 8 mg dose per month of the weekly formulation of buprenorphine prolonged-release injection was allowed. Addiction counselling was provided at each weekly and monthly visit, and additional counselling visits were accommodated as needed.</p> <p>^e Responder rate; defined as no evidence of illicit opioid use at pre-specified time points within the study.</p> <p>References: ¹ Lofwall MR, Walsh SL, Nunes EV et al. (2018) Weekly and monthly buprenorphine prolonged-release injection depot formulations vs daily sublingual buprenorphine and naloxone for treatment of opioid use disorder. JAMA Internal Medicine 178: 764–73</p> <p>Abbreviations: RCT, randomised controlled trial</p>						

Appendix B: Results tables

Lofwall et al. (2018)

	Buprenorphine prolonged-release injection	Sublingual buprenorphine-naloxone	Analysis
n	213	215	
Primary outcomes			
Mean percentage of urine samples negative for illicit opioids for weeks 1 to 24	35.1%	28.4%	Treatment difference 6.7% (95% CI -0.1 to 13.6, p<0.001 [non-inferiority]) ^a
Responder rate ^b	17.4% (37/213)	14.4% (31/215)	Treatment difference 3.0% (95% CI -4.0 to 9.9, p<0.001 [non-inferiority]) ^c
Selected secondary outcomes			
Opioid-negative urine samples examined by a CDF for weeks 4 to 24 (affirmed by self-report of no illicit opioid use)			
Median	27.6%	0.0%	p=0.004 for superiority of buprenorphine prolonged-release injection compared with sublingual buprenorphine-naloxone.
Mean	35.1%	26.7%	
Proportion of people still in the study at week 24	69.0% (147/213)	72.6% (156/215)	Treatment difference -3.5% (95% CI -12.2 to 5.1, p=0.009 [non-inferiority]) ^d
Selected exploratory outcomes			

	Buprenorphine prolonged-release injection	Sublingual buprenorphine-naloxone	Analysis
Proportion of people receiving additional 8 mg doses of buprenorphine injection	14/213 (6.6%) (23 doses in total)	17/215 (7.9%) (28 doses in total)	No statistical analysis reported
Mean attendance at counselling during scheduled study visits	96.1% (range 97% to 100%)	94.1% (range 84% to 98%)	No statistical analysis reported
Need-to-use opioids VAS	Results reported graphically only	Results reported graphically only	The authors report that there was no significant difference between the groups
Clinical opiate withdrawal scale	Results reported graphically only	Results reported graphically only	The authors report that there was no significant difference between the groups
Safety and tolerability outcomes			
n	213	215	
Percentage of participants experiencing any adverse event	60.1% (128/213)	55.3% (119/215)	No statistical analysis reported
Percentage of participants experiencing 1 or more drug-related adverse event	32.9% (70/213)	29.8% (64/215)	No statistical analysis reported
Percentage of participants experiencing nonfatal serious adverse events	2.3% (5/213)	6.0% (13/215)	No statistical analysis reported
Percentage of participants who discontinued treatment because of adverse events	3.3% (7/213)	1.4% (3/215)	No statistical analysis reported
Percentage of participants experiencing injection site pain	8.9% (19/213)	7.9% (17/215)	No statistical analysis reported

	Buprenorphine prolonged-release injection	Sublingual buprenorphine-naloxone	Analysis
<p>^a Buprenorphine prolonged-release injection was shown to be non-inferior to sublingual buprenorphine-naloxone because the lower limit of the 95% CI was within the 11% pre-specified non-inferiority margin</p> <p>^b See terms used in this evidence review for definition of responder rate</p> <p>^c Buprenorphine prolonged-release injection was shown to be non-inferior to sublingual buprenorphine-naloxone because the lower limit of the 95% CI was within the 10% pre-specified non-inferiority margin</p> <p>^d Buprenorphine prolonged-release injection was shown to be non-inferior to sublingual buprenorphine-naloxone because the lower limit of the 95% CI was within the 15% pre-specified non-inferiority margin</p>			
<p>Abbreviations: CDF, cumulative distribution frequency; CI, confidence interval; VAS, visual analogue scale</p>			

Appendix C: Quality assessment of included studies

Quality assessment question	Lofwall et al. (2018)
Did the trial address a clearly focused issue?	yes
Was the assignment of patients to treatments randomised?	yes ^a
Were patients, health workers and study personnel blinded?	yes ^b
Were the groups similar at the start of the trial?	yes
Aside from the experimental intervention, were the groups treated equally?	yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	yes
How large was the treatment effect?	See results table
How precise was the estimate of the treatment effect?	See results table
Can the results be applied in your context? (or to the local population)	unclear ^c
Were all clinically important outcomes considered?	yes ^d
Are the benefits worth the harms and costs?	See overview
^a Participants were randomised using a centralised computer system. It would appear that allocation to treatment was concealed.	
^b Unblinded staff not participating in study evaluations dispensed and administered subcutaneous injections to avoid the risk of unblinding because of small differences in the appearance of active and placebo injections.	
^c The study was completed solely in the US and so the results may be less applicable to treatment in a UK setting. However the most common opioid misused by participants at baseline was heroin which reflects the UK population where heroin is the main problem drug of most adult drug misusers. Participants were provided with expenses (mean payment of \$50 per study visit) to attend study follow-up visits. Attendance at follow-up visits may be lower in a real-world setting where people are not incentivised to attend.	
^d It appears that all relevant outcomes were considered. However some important patient-orientated outcomes such as desire- and need-to-use opioids, and withdrawal symptoms were only covered as exploratory outcomes.	
Checklist used: CASP RCT checklist	

Appendix D: Literature search strategy

Database: Medline

Platform: Ovid

Version: 1946 to August 1 2018

Search date: 02/08/2018

Number of results retrieved: 133

Search strategy:

Database: Ovid MEDLINE(R) <1946 to August 1, 2018>

Search Strategy:

-
- 1 Buprenorphine/ (4604)
 - 2 (buprenorphine or CAM2038 or CAM 2038 or CAM-2038).tw. (5020)
 - 3 (probuphine or sublocade).tw. (3)
 - 4 or/1-3 (5720)
 - 5 (depot or long or slow or subcutaneous or implant* or delay* or subdermal).tw. (1957202)
 - 6 delayed-action preparations/ or drug implants/ (41766)
 - 7 Injections, Subcutaneous/ (31235)
 - 8 or/5-7 (1996719)
 - 9 (month* or week*).tw. (2041131)
 - 10 4 and 8 and 9 (221)
 - 11 exp Opioid-Related Disorders/ (23028)
 - 12 ((opiod* or opiate* or heroin or morphine or opium) adj4 (disorder* or abuse* or addict* or dependen* or use* or usage*)).tw. (30623)
 - 13 11 or 12 (40583)
 - 14 10 and 13 (154)
 - 15 animals/ not humans/ (4447618)
 - 16 14 not 15 (146)
 - 17 limit 16 to english language (133)

Database: Medline in-process

Platform: Ovid

Version: August 1 2018

Search date: 02/08/2018

Number of results retrieved: 29

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 1, 2018>

Search Strategy:

-
- 1 Buprenorphine/ (0)
 - 2 (buprenorphine or CAM2038 or CAM 2038 or CAM-2038).tw. (563)
 - 3 (probuphine or sublocade).tw. (7)
 - 4 or/1-3 (563)
 - 5 (depot or long or slow or subcutaneous or implant* or delay* or subdermal).tw. (252409)
 - 6 delayed-action preparations/ or drug implants/ (0)
 - 7 Injections, Subcutaneous/ (0)
 - 8 or/5-7 (252409)
 - 9 (month* or week*).tw. (209623)
 - 10 4 and 8 and 9 (42)
 - 11 exp Opioid-Related Disorders/ (0)

12 ((opioid* or opiate* or heroin or morphine or opium) adj4 (disorder* or abuse* or addict* or dependen* or use* or usage*)).tw. (3713)

13 11 or 12 (3713)

14 10 and 13 (30)

15 animals/ not humans/ (0)

16 14 not 15 (30)

17 limit 16 to english language (29)

Database: Medline epubs ahead of print

Platform: Ovid

Version: August 1 2018

Search date: 02/08/2018

Number of results retrieved: 6

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <August 1, 2018>

Search Strategy:

1 Buprenorphine/ (0)

2 (buprenorphine or CAM2038 or CAM 2038 or CAM-2038).tw. (145)

3 (probuphine or sublocade).tw. (1)

4 or/1-3 (145)

5 (depot or long or slow or subcutaneous or implant* or delay* or subdermal).tw. (42138)

6 delayed-action preparations/ or drug implants/ (0)

7 Injections, Subcutaneous/ (0)

8 or/5-7 (42138)

9 (month* or week*).tw. (44008)

10 4 and 8 and 9 (6)

11 exp Opioid-Related Disorders/ (0)

12 ((opioid* or opiate* or heroin or morphine or opium) adj4 (disorder* or abuse* or addict* or dependen* or use* or usage*)).tw. (866)

13 11 or 12 (866)

14 10 and 13 (6)

15 animals/ not humans/ (0)

16 14 not 15 (6)

17 limit 16 to english language (6)

Database: Medline daily update

Platform: Ovid

Version: August 1 2018

Search date: 02/08/2018

Number of results retrieved: 1

Search strategy:

Database: Ovid MEDLINE(R) Daily Update <August 1, 2018>

Search Strategy:

1 Buprenorphine/ (2)

2 (buprenorphine or CAM2038 or CAM 2038 or CAM-2038).tw. (3)

3 (probuphine or sublocade).tw. (0)

4 or/1-3 (3)

5 (depot or long or slow or subcutaneous or implant* or delay* or subdermal).tw. (1770)

Evidence review: Opioid dependence: buprenorphine prolonged-release injection (Buvidal) (February 2019)

6 delayed-action preparations/ or drug implants/ (33)
7 Injections, Subcutaneous/ (10)
8 or/5-7 (1796)
9 (month* or week*).tw. (1865)
10 4 and 8 and 9 (1)
11 exp Opioid-Related Disorders/ (19)
12 ((opiod* or opiate* or heroin or morphine or opium) adj4 (disorder* or abuse* or addict* or dependen* or use* or usage*)).tw. (33)
13 11 or 12 (37)
14 10 and 13 (1)
15 animals/ not humans/ (1822)
16 14 not 15 (1)
17 limit 16 to english language (1)

Database: Embase

Platform: Ovid
Version: 1974 to 2018 August 01
Search date: 02/08/2018
Number of results retrieved: 325
Search strategy:

Database: Embase <1974 to 2018 August 01>
Search Strategy:

1 Buprenorphine/ (15209)
2 (buprenorphine or CAM2038 or CAM 2038 or CAM-2038).tw. (7972)
3 (probuphine or sublocade).tw. (27)
4 or/1-3 (16052)
5 (depot or long or slow or subcutaneous or implant* or delay* or subdermal).tw. (2911638)
6 long acting drug/ or delayed release formulation/ or sustained release preparation/ (27279)
7 subcutaneous drug administration/ or drug implant/ (101414)
8 or/5-7 (2997463)
9 (month* or week*).tw. (3370568)
10 4 and 8 and 9 (623)
11 opiate addiction/ (15481)
12 ((opiod* or opiate* or heroin or morphine or opium) adj4 (disorder* or abuse* or addict* or dependen* or use* or usage*)).tw. (49595)
13 11 or 12 (55827)
14 10 and 13 (350)
15 nonhuman/ not human/ (4205887)
16 14 not 15 (341)
17 limit 16 to english language (325)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley
Version:
CDSR – Issue 8 of 12, August 2018
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – Issue 7 of 12, July 2018
HTA – 4 of 4, October 2016 (legacy database)
NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 02/08/2018

Number of results retrieved: CDSR 18; DARE 0; CENTRAL 155; HTA -0; NHS EED 0 -.

Search Name: buprenorphine

Date Run: 02/08/18 14:06:10.259

Description:

ID SearchHits

#1 MeSH descriptor: [Buprenorphine] this term only 1010

#2 buprenorphine or CAM2038 or CAM 2038 or CAM-2038:ti,ab,kw (Word variations have been searched) 2047

#3 probuphine or sublocade:ti,ab,kw (Word variations have been searched) 2

#4 {or #1-#3} 2047

#5 depot or long or slow or subcutaneous or implant* or delay* or subdermal:ti,ab,kw (Word variations have been searched) 220176

#6 MeSH descriptor: [Delayed-Action Preparations] this term only 5579

#7 MeSH descriptor: [Drug Implants] this term only 440

#8 MeSH descriptor: [Injections, Subcutaneous] this term only 3545

#9 {or #5-#8} 220176

#10 month* or week*:ti,ab,kw (Word variations have been searched) 446091

#11 #4 and #9 and #10 200

#12 MeSH descriptor: [Opioid-Related Disorders] explode all trees 1801

#13 (opiod* or opiate* or heroin or morphine or opium) near/4 (disorder* or abuse* or addict* or dependen* or use* or usage*):ti,ab,kw (Word variations have been searched) 8423

#14 #12 or #13 8423

#15 #11 and #14 173

Trials registry search strategies

Clinicaltrials.gov

Search date: 08/08/2018

Number of results retrieved: 40

Search strategy:

weekly OR monthly OR depot Or implant OR subcutaneous | (opiod OR opiate OR heroin) AND (dependence OR abuse OR misuse) | buprenorphine or CAM2038 OR probuphine OR sublocade | Phase 3, 4

Clinicaltrialsregister.eu

Search date: 09/08/2018

Number of results retrieved: 0

Search strategy: buprenorphine or CAM2038 or probuphine or sublocade

Appendix E: Studies excluded and not-prioritised

A literature search for buprenorphine long-acting preparations was conducted which identified 419 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and 35 references were obtained and assessed for relevance to the buprenorphine prolonged-release injection (Buvidal) product. Those references related to other long-acting buprenorphine products that are not currently available in the UK were excluded.

One phase 3 randomised controlled trial ([Lofwall et al. 2018](#)) identified from the search was included in this evidence review. An additional open-label, 48-week safety study has completed but results have not been published yet ([NCT02672111](#)). A summary of the included studies is shown in [appendix A](#). The excluded studies are listed in the following table.

Study reference	Reason for exclusion or non-prioritisation
Albayaty M, Linden M, Olsson H et al. (2017). Pharmacokinetic Evaluation of Once-Weekly and Once-Monthly Buprenorphine Subcutaneous Injection Depots (CAM2038) Versus Intravenous and Sublingual Buprenorphine in Healthy Volunteers Under Naltrexone Blockade: An Open-Label Phase 1 Study. <i>Advances in Therapy</i> , 34: 560–75	Study not prioritised (not the best available evidence)
Bailey GL. (2013). Twelve month outcomes with buprenorphine implants for opioid dependence. <i>CNS Spectrums</i> , 18: 372	Poor relevance against search terms (wrong intervention)
Beebe K, Rotrosen J, Ling W et al. (2010). A single cross-over, open-label study of the relative bioavailability of buprenorphine implants versus suboxone in patients with opioid dependence. <i>Neuropsychopharmacology</i> : S383	Poor relevance against search terms (wrong intervention)
Beebe KL, Chavoustie S, Ling W et al. (2012). Buprenorphine implants for the treatment of opioid dependence: Six and 12 month outcomes. <i>Neuropsychopharmacology</i> : S266–7	Poor relevance against search terms (wrong intervention)
Carter J, Dammerman R, and Frost M (2017). Health economics of probuphine Vs. Oral buprenorphine, injectable naltrexone, or methadone for opioid dependence. <i>American Journal on Addictions</i> 26: 293	Poor relevance against search terms (wrong intervention)
Carter JA, Dammerman R, Tiberg F et al. (2017). Cost-effectiveness of long acting injectable buprenorphine versus sublingual buprenorphine to treat opioid use disorder in Sweden and the United Kingdom. <i>Value in health. Conference: ISPOR 22nd annual international meeting. United states</i> , 20: A304	Unpublished study
Carter JA, Dammerman R, and Frost M (2017). Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. <i>Journal of Medical Economics</i> , 20: 893–901	Poor relevance against search terms (wrong intervention)
Frost M, and Bobb R (2018). Buprenorphine Implant Removal 7 Years Postinsertion: A Case Report. <i>Journal of Addiction Medicine</i> 26: 26	Poor relevance against search terms (wrong intervention)
Gowing L, Ali R, White JM et al. (2017). Buprenorphine for managing opioid withdrawal. <i>Cochrane Database of Systematic</i>	Poor relevance against search terms (wrong intervention)

Study reference	Reason for exclusion or non-prioritisation
Reviews Issue 2. Art. No.: CD002025. DOI: 10.1002/14651858.CD002025.pub5	
Haasen C, Linden M, and Tiberg F (2017). Pharmacokinetics and pharmacodynamics of a buprenorphine subcutaneous depot formulation (CAM2038) for once-weekly dosing in patients with opioid use disorder. <i>Journal of Substance Abuse Treatment</i> 78: 22–9	Study not prioritised (not the best available evidence)
Haight B, Andorn A, Laffont C et al. (2017). RBP-6000 buprenorphine monthly depot demonstrates sustained clinical efficacy and safety in phase III opioid use disorder trials. <i>Neuropsychopharmacology</i> 43: S463–4	Unpublished study
Iltzoe M, and Guarnieri M. (2017). New developments in managing opioid addiction: Impact of a subdermal buprenorphine implant. <i>Drug Design, and Development and Therapy</i> 11: 1429–37	Poor relevance against search terms (wrong intervention)
Jensen R, Carter J A, Tiberg F et al. (2017). Flexible-dose depot buprenorphine injection for opioid substitution treatment in heroin-addicted adults: A Swedish pharmacoeconomic perspective. <i>Value in Health</i> 20: A711	Poor relevance against search terms (non-relevant population)
Jia H, Greenwald M K, Vince BD et al. (2015). A multiple-dose study of blockade of opioid subjective effects by subcutaneous injections of depot buprenorphine in subjects with opioid use disorder. <i>Clinical Pharmacology and Therapeutics</i> 1: S75	Unpublished study
Jones AK, Ngaimisi E, Gopalakrishnan M et al. (2017). Long-term exposure of RBP-6000 buprenorphine monthly formulation for the treatment of opioid use disorder: A combined population pharmacokinetic analysis. <i>Journal of Pharmacokinetics and Pharmacodynamics</i> 44: S50–1	Unpublished study
Laffont C M, Gomeni R, Heidbreder C et al. (2016). Population pharmacokinetic modeling after repeated administrations of rbp-6000, a new, subcutaneous formulation of buprenorphine for the treatment of opioid use disorder. <i>Clinical Pharmacology and Therapeutics</i> 1: S70	Unpublished study
Laffont C M, Gomeni R, Heidbreder C et al. (2016). Population Pharmacokinetic Modeling After Repeated Administrations of RBP-6000, a New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Use Disorder. <i>Journal of Clinical Pharmacology</i> 56: 806–15	Study not prioritised (not the best available evidence)
Nasser A, Heidbreder C, Fudala PJ et al. (2014). A model-based approach to evaluate the pk and mu-opioid receptor occupancy of RBP-6000, a once monthly depot formulation of buprenorphine. <i>Clinical Pharmacology and Therapeutics</i> 1: S81	Unpublished study
Nasser AF, Greenwald M K, Vince B et al. (2016). Sustained-Release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge With Hydromorphone in Subjects With Opioid Use Disorder. <i>Journal of Clinical Psychopharmacology</i> 36: 18–26	Poor relevance against search terms (phase 2 study)
Ngaimisi E, Gopalakrishnan M, Ivaturi V et al. (2017). Exposure-response analyses to support dosing recommendations for RBP-6000 buprenorphine monthly formulation in subjects with opioid use disorder. <i>Journal of Pharmacokinetics and Pharmacodynamics</i> 44: S50	Unpublished study
Rosenthal RN, Ling W, Casadonte P et al. (2013). Buprenorphine implants for treatment of opioid dependence: randomized	Poor relevance against search terms (wrong intervention)

Study reference	Reason for exclusion or non-prioritisation
comparison to placebo and sublingual buprenorphine/naloxone. <i>Addiction</i> 108: 2,141–9	
Rosenthal R, Kim S, Lofwall M et al. (2017). A randomized trial of buprenorphine implants in adults stabilized on sublingual buprenorphine. <i>American Journal on Addictions</i> 26: 265–6	Poor relevance against search terms (wrong intervention)
Rosenthal R, Lofwall M R, Kim S et al. (2017). Sensitivity analysis of a comparative trial of 6 month buprenorphine implants (probuphine) and sublingual buprenorphine in stable opioid-dependent patients. <i>Drug and Alcohol Dependence</i> 171: e179	Poor relevance against search terms (wrong intervention)
Saxon AJ, Hser YI, Woody G et al. (2013). Medication-assisted treatment for opioid addiction: methadone and buprenorphine. <i>Journal of Food & Drug Analysis</i> 21: S69–72	Poor relevance against search terms (wrong intervention)
Schmith VD, Curd L, Lohmer LR et al. (2018). Evaluation of RBP-6000 effects on qt interval during treatment for opioid use disorder. <i>Clinical Pharmacology and Therapeutics</i> 103: S96	Unpublished study
Sharma M, Kalsi V, and Kaur B (2018). Subdermal buprenorphine implant: Suitable alternative in the management of opioid addiction. <i>Asian Journal of Pharmaceutical and Clinical Research</i> 11: 110	Poor relevance against search terms (wrong intervention)
Sigmon SC, Wong CJ, Chausmer AL et al. (2004). Evaluation of an injection depot formulation of buprenorphine: placebo comparison. <i>Addiction (abingdon, and England)</i> 99: 1439–49	Poor relevance against search terms (wrong intervention)
Sigmon SC, Moody DE, Nuwayser ES et al. (2006). An injection depot formulation of buprenorphine: extended bio-delivery and effects. <i>Addiction</i> 101: 420–3	Poor relevance against search terms (wrong intervention)
Sobel BF, Sigmon SC, Walsh SL et al. (2004). Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. <i>Drug & Alcohol Dependence</i> 73: 11–22	Poor relevance against search terms (wrong intervention)
Tiberg F, Jensen R, Sanjurjo V et al. (2017). Substitution therapy with flexible-dose depot buprenorphine injection to treat opioid use disorder in the United Kingdom: A pharmacoeconomic assessment. <i>Value in Health</i> 20: A711	Unpublished study
Wallace L, and Kadakia A. (2016). Buprenorphine transdermal system (butrans) utilization. <i>Postgraduate Medicine</i> 128: 94–5	Poor relevance against search terms (wrong intervention)
Walsh S. (2017). Novel formulations of buprenorphine for the treatment of opioid use disorder. <i>Neuropsychopharmacology</i> 43: S62	Unpublished study
Walsh SL, Comer SD, Lofwall MR et al. (2017). Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder: A Randomized Clinical Trial. <i>JAMA Psychiatry</i> 74: 894–902	Study not prioritised (not the best available evidence)
White J, Bell J, Saunders JB et al. (2009). Open-label dose-finding trial of buprenorphine implants (Probuphine) for treatment of heroin dependence. <i>Drug & Alcohol Dependence</i> 103: 37–43	Poor relevance against search terms (wrong intervention)