
buprenorphine 8/16/24/32/64/96/128 mg prolonged-release solution for injection (Buvidal®)

Camurus AB

5 July 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

buprenorphine (Buvidal®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: Use in patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate.

In a phase III study in patients with opioid dependence, subcutaneous buprenorphine was non-inferior to sublingual buprenorphine/naloxone for the mean percentage of urine samples with test results negative for illicit opioids.

Chairman
Scottish Medicines Consortium

Indication

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.^{1, 2}

Dosing Information

Buvidal® is intended for subcutaneous (SC) administration only. It should be injected slowly and completely into the subcutaneous tissue of different areas. Administered dose should be as a single injection and not divided.

Administration is restricted to healthcare professionals. Appropriate precautions, such as to conduct patient follow-up visits with clinical monitoring according to the patient's needs, should be taken when prescribing and dispensing buprenorphine. Take-home use or self-administration of the product by patients is not allowed. To avoid precipitating symptoms of withdrawal, treatment should be started when objective and clear signs of mild to moderate withdrawal are evident.

Initiation of treatment in patients not already receiving buprenorphine

Patients should receive a sublingual (SL) buprenorphine 4mg dose and be observed for an hour before the first administration of weekly Buvidal® to confirm tolerability to buprenorphine. The recommended starting dose is 16mg, with one or two additional 8mg doses at least 1 day apart, to a target dose of 24mg or 32mg during the first treatment week. 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 after treatment initiation with weekly Buvidal®, once patients have been stabilised on weekly treatment (4 weeks or more, where practical).

Switching from sublingual buprenorphine products

Patients may be switched directly to weekly or monthly Buvidal®, starting on the day after the last daily buprenorphine sublingual treatment dose. See Summary of Product Characteristics (SPC) for dosing recommendations.

Maintenance treatment and dose adjustments

Buvidal® can be administered weekly or monthly. Doses may be increased or decreased and patients can be switched between weekly and monthly products according to individual patient's needs and treating physician's clinical judgement. Assessment of long-term treatment is based on 48-week data. A maximum of one supplemental 8mg dose may be administered at an unscheduled visit between regular weekly and monthly doses, based on individual patient's temporary needs. The maximum dose per week for patients who are on weekly treatment is 32mg with an additional 8mg dose. The maximum dose per month for patients who are on monthly treatment is 128mg with an additional 8mg dose.

Further details are included in the SPC.^{1, 2}

Product availability date

January 2019

Summary of evidence on comparative efficacy

Buprenorphine is a partial agonist that binds to the μ (mu) and κ (kappa) opioid receptors in the brain which may lead to a reduction in the use of illicit opioids in patients with opioid dependence. It is currently available to treat opioid dependence in sublingual (SL) and oromucosal preparations. The submitting company has requested that SMC considers this product when positioned for use in patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate.

Key evidence for this indication is from HS-11-421, a randomised, double-blind, active-controlled, phase III study. This study recruited adult patients aged 18 to 65 who had been diagnosed with, and were looking for treatment for, moderate-to-severe opioid use disorder (n=428). This was defined according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition diagnostic criteria for opioid use disorder which includes 11 symptoms (mild: 2 to 3 symptoms, moderate: 4 to 5 symptoms or severe: ≥ 6 symptoms present). Recruited patients had to be deemed appropriate for treatment with buprenorphine based on medical and psychosocial history. They were required to be willing to use regular contraception.^{3,4}

On the day of randomisation, all eligible patients who were in opioid withdrawal were given an open-label dose of SL buprenorphine 4mg and naloxone 1mg. Patients who tolerated this were randomised equally to receive subcutaneous (SC) injections of buprenorphine (n= 213) or SL buprenorphine/naloxone (n=215), both with matched placebo. In week 0, doses were titrated up to 32mg/week for SC buprenorphine or 24mg/day for SL buprenorphine. In weeks 1 to 11 (phase 1), patients had weekly visits to receive SC buprenorphine or placebo injections and a 1-week supply of SL buprenorphine/naloxone or placebo. SC buprenorphine weekly doses of 16mg, 24mg, or 32mg, were estimated to be approximately equal to SL buprenorphine hydrochloride 8mg, 16mg, and 24mg per day, respectively. In weeks 12 to 24 (phase 2) patients visited monthly, with monthly SC buprenorphine or placebo injections and a 4-week supply of SL buprenorphine-naloxone or SL placebo. SC buprenorphine monthly doses of 64mg, 96mg, 128mg, or 160mg, were estimated to be approximately equal to SL buprenorphine hydrochloride 8mg, 16mg, 24mg, and 32mg per day, respectively. An additional dose of 8mg per week of open-label SC buprenorphine was allowed in both groups in the second part of the study if deemed necessary by the investigator. Doses could be adjusted (blinded) as needed at scheduled visits. Addiction counselling was given at all scheduled visits. Additional visits for counselling and other medical concerns were allowed. Standard clinical care was offered until follow up at week 28.³

Two primary outcomes were included due to different analyses requested by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). The study aimed to demonstrate non-inferiority of SC buprenorphine compared with SL buprenorphine/naloxone.

The EMA primary outcome was the mean percentage of urine samples with test results negative for illicit opioids for weeks 1 to 24. For the FDA, the primary outcome was responder rate. A responder was defined as no evidence of illicit opioid use by having a negative urine test result and no self-reported drug use at pre-specified times (in phase 1 at week 12 and for at least 2 of 3 assessments at weeks 9 to 11 and in phase 2 for at least 5 of 6 assessments from weeks 12 to 24, including month 6 (that is weeks 21-24). Urine samples were collected with temperature verification at each scheduled visit and at three additional randomly scheduled visits in phase 2.³

In the intention-to-treat population (ITT), defined as all randomised patients, both primary outcomes met pre-specified criteria for non-inferiority. The least squares (LS) mean percentage of negative urine samples (week 1 to 24) was 35% in the SC buprenorphine group and 28% in the SL buprenorphine/naloxone group. The difference between groups was 6.7% (95% confidence interval [CI]: -0.1 to 13.6, $p < 0.001$), non-inferiority was declared as this was within the pre-specified margin of 11%.^{3, 4} In the SC buprenorphine group, 17% of patients were responders compared with 14% in the SL buprenorphine/naloxone group, difference 3% (95% CI: -4 to 9.9, $p < 0.001$). Again, non-inferiority was declared as this was within the pre-specified margin of 10%.^{3, 4}

In a post hoc sensitivity analysis, in the subgroup of patients taking prescription opioids as their primary opioid at initiation, non-inferiority of SC buprenorphine to SL buprenorphine/naloxone was not demonstrated (treatment difference -11.6 % [95% CI: -24.6 to 1.5]). However, in patients taking heroin as their primary opioid the treatment effect favours SC buprenorphine (treatment difference 14.8%, 95% CI: 8.0 to 21.7).⁴

The first secondary outcome, mean percentage of opioid-negative urine samples with patients' self-reporting of opioid use, examined by a cumulative distribution function (CDF) for weeks 4 to 24 was 35% in the SC buprenorphine group and 27% in the SL buprenorphine/naloxone group.^{3, 4} Study retention was the other secondary outcome. At week 12, retention was 80% and 79%, at week 24 retention was 69% and 73%, and at week 28 (follow-up) it was 57% and 59% in the SC buprenorphine and SL buprenorphine/naloxone groups respectively.³ There was no statistical difference between groups for the use of other drugs of abuse (barbiturates, amphetamine, phencyclidine or marijuana) at any time point.⁴

Mean visual analogue scale (VAS) scores for morning cravings were similar between groups at week 2, decreased in both groups between week 2 and 12 and remained relatively stable until week 25. Generally morning cravings were similar between groups.⁴

Summary of evidence on comparative safety

The EMA generally concluded that the number and type of adverse events were comparable between SC buprenorphine and other treatments with the exception of injection site reactions.⁴

HS-11-421

In study HS-11-421 at least one treatment emergent adverse event (TEAE) was reported in 60% of patients in the SC buprenorphine group and 55% of the SL buprenorphine/naloxone group. These were thought to be drug related in 33% and 30% of the SC buprenorphine and SL buprenorphine/naloxone groups respectively. No drug overdoses were reported in the SC buprenorphine group compared with 2.3% of the SL buprenorphine/naloxone group. Fewer patients were admitted to hospital in the SC buprenorphine group (1.4% versus 5.6%). The most common reason for admission to hospital was for infections that may have been related to injection drug use (1 patient in the SC buprenorphine group and 5 patients in the SL buprenorphine/naloxone group). The most common adverse events in the key study were injection site pain (8.9% and 7.9% of the SC buprenorphine and SL buprenorphine/naloxone groups respectively), headache (7.5% and 7.9%), constipation (7.5% and 7.4%), and nausea (7.0% and 7.9%).

HS-14-499

HS-14-499 was an open-label study that aimed to assess long-term safety of SC buprenorphine in adult patients with opioid use disorder. The safety population included 227 patients who received at least one dose of study medication. Inclusion and exclusion criteria were similar to HS-11-421 however patients who were currently receiving sublingual buprenorphine or buprenorphine/naloxone were also eligible. Patients received weekly or monthly SC buprenorphine for up to 48 weeks. They could transfer between weekly and monthly buprenorphine as per conversion guidelines. After this period patients received SL buprenorphine or buprenorphine/naloxone for 4 weeks of follow up. No additional serious safety concerns were identified however there were differences in injection site TEAEs.^{4, 5} In the group of patients who were receiving SL buprenorphine or buprenorphine/naloxone prior to study entry (n=190), 69% had at least one TEAE and 23% had an injection site TEAE. In the patients who were new to buprenorphine (n=37), 32% had a TEAE and 5.4% had an injection site TEAE.^{5, 6}

Summary of clinical effectiveness issues

Opioid dependence significantly impacts patients, their families and society in general. It is a chronic relapsing/remitting condition that requires long-term treatment. A key aim of treatment is to reduce/discontinue illicit opioid use as this assists patients in improving physical and mental health, and psychosocial functioning. Drug misuse treatment involves offering a range of psychosocial treatment and support interventions, not just prescribing. Regarding pharmacological treatment, methadone was the first medicine to be used in opioid dependence and is widely used. Buprenorphine is also an established and commonly used maintenance treatment.^{4, 7} Methadone,

buprenorphine and lofexidine are also all effective in detoxification.⁷ Buprenorphine/naloxone SL tablets (SMC 355/07) and buprenorphine oral lyophilisate (SMC 1245/17) have been accepted by SMC for restricted use in patients for whom methadone is not suitable. Methadone and SL buprenorphine are usually administered daily under supervision, at least initially, which may be inconvenient for patients and impact the health service. The SC depot preparation of buprenorphine was developed to improve adherence, avoid misuse, improve safety, prevent potential access by children, and reduce the burden of daily administration.⁴

The submitting company has requested that SMC considers this product when positioned for use in patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate. Clinical experts consulted by SMC considered that SC buprenorphine fills an unmet need in this therapeutic area as it provides a long-acting treatment option.

Non-inferiority of SC buprenorphine compared with SL buprenorphine/naloxone was demonstrated in the key study HS-11-421 for the two primary outcomes: mean percentage of urine samples with test results negative for illicit opioids and responder rate.

The key study compared SC buprenorphine with SL buprenorphine/naloxone. There is no comparison with SL buprenorphine which experts consider is also a relevant comparator. The EMA considered that buprenorphine/naloxone was an acceptable comparator as naloxone does not affect the pharmacodynamic properties of buprenorphine and is added to try to prevent misuse of the medication. In a post hoc sensitivity analysis in the subgroup of patients taking prescription opioids at initiation, non-inferiority of SC buprenorphine to SL buprenorphine/naloxone was not demonstrated. However, in patients taking heroin, the treatment effect favours SC buprenorphine.⁴

Patients were given weekly then monthly supplies of SL buprenorphine in the key study; adherence to this was not assessed. The duration of treatment was 25 weeks which may be relatively short to demonstrate outcomes in a potentially long term condition. Data are available for treatment of up to 12 months; however, this is from an open-label safety study, HS-14-499.⁴

The key study was conducted in the USA. Heroin was the primary opioid for around 70% of patients with the others being prescription opioids. Addiction to prescription opioids may be less prevalent in the Scottish population. Treatment with SC buprenorphine is intended for use in adults and adolescents aged 16 years or over; data are not available for patients aged under 18 or over 65 years. Patients had moderate-to-severe opioid use disorder so the study results may not be applicable to patients diagnosed with mild opioid use disorder. Patients were excluded if they had received pharmacotherapy for opioid use disorder in the last 60 days. This could affect the generalisability to patients who are already receiving treatment and a change in treatment is being considered. Patients received weekly then monthly counselling sessions which may not be reflective of Scottish practice.

The introduction of SC buprenorphine would provide an additional treatment option for patients with opioid dependence. Clinical experts consulted by SMC considered that SC buprenorphine is a therapeutic advancement due to its long duration of action. It would potentially reduce the impact on the patient and community pharmacy services as it is administered weekly or monthly compared with SL buprenorphine which is administered daily, often under supervision. SC buprenorphine would, however, require administration by a healthcare professional. Clinical experts considered that the place in therapy could be in patients who have difficulty attending daily pharmacy visits, for example due to mobility problems, those working or in education, family commitments, or irregular attendance. The reduced frequency of administration could support social integration. SC buprenorphine would also remove storage of controlled drugs in patients' homes. The clinical experts considered that it may also be useful where an alternative to oral administration would be preferable for example in prisons where there is a high risk of drug diversion.

Summary of comparative health economic evidence

The company submitted a cost minimisation analysis comparing SC buprenorphine to SL buprenorphine/naloxone, within a framework of medical, social and psychological treatment, for the treatment of opioid dependence in adults and adolescents aged 16 years or over. The company has requested that SC buprenorphine is considered by SMC when positioned for use in patients whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate. Based on SMC expert responses the comparator is appropriate, but SL buprenorphine was also considered to be an appropriate comparator.

A five state Markov model was submitted using a 1 year time horizon. Health states were defined according to whether patients were on/off treatment and using/not using illicit opioids. For patients on treatment, the model further captured patients' injection status i.e. injecting or not injecting illicit opioids. The clinical data used in the economics were taken from a subgroup analysis that excluded patients addicted to prescription opioids.⁷ The company justified this analysis on the basis that this subgroup is likely to reflect the relevant patient population in Scotland. The model assumed no difference in efficacy between treatments in terms of retention or illicit opioid use, two of the key clinical parameters. However, differences in probability of hospitalisation were included (0.08% and 0.30% for SC buprenorphine and SL buprenorphine naloxone respectively).

Medicine acquisition costs, administration costs and monitoring/supervision costs were included in the analysis. Patients receiving SC buprenorphine were assumed to receive treatment once weekly for the first 4 weeks and then monthly thereafter. Administration was assumed to take 10 minutes and carried out by a substance abuse clinic nurse. In relation to SL buprenorphine/naloxone, the company assumes that health boards in Scotland currently pay a fixed monthly fee of £72 per patient (regardless of the frequency of visits). This fixed fee was assumed to cover dispensing and supervised consumption fees. Differences in hospitalisation costs were included in the analysis. No adverse events were included.

The base case and key scenario analyses results are outlined in the Table below.

Table 1: Base case results

Treatment	Medicine acquisition cost	Administration/ pharmacy cost	Other health resource use	Total costs
SC buprenorphine	£1,997	£108	£4,178	£6,283
SL buprenorphine naloxone	£1,562	£561	£4,300	£6,423
Incremental cost/saving	£436	-£454	-£122	-£140

Table 2: Scenario analyses results

Scenario	Total costs (SC buprenorphine)	Total costs (SL buprenorphine naloxone)	Incremental cost/saving
1. Fee per supervision assumed for SL buprenorphine naloxone	£6,283	£6,288	-£5
2. Difference in hospitalisations removed	£7,687	£7,705	-£18
3. Combined scenario analysis (fee per supervision assumed for SL buprenorphine naloxone and difference in hospitalisations removed)	£7,687	£7,570	£117
4. Scenario 3 plus assumption that 25% of patients remain on weekly SC buprenorphine	£7,740	£7,570	£170
5. Comparison against SL buprenorphine (assumes fee per supervision for SL buprenorphine and removes differences in hospitalisations between treatments)	£7,687	£7,476	£213
6. Scenario 5 plus assumption that 25% of patients remain on weekly SC buprenorphine	£7,740	£7,475	£265

There were a number of weaknesses with economic analysis, including the following;

- There may be some uncertainty surrounding the comparator used in the base case. SMC experts have indicated that SL buprenorphine may also be a treatment that is displaced in practice. For completeness the company was asked to provide the results of an analysis which compares SC buprenorphine to buprenorphine SL (see scenario 5 above). This results in SC buprenorphine being the more expensive treatment.
- The fee structure used for SL buprenorphine/naloxone in the base case is subject to some uncertainty. Based on expert responses, the current approach to supervision for patients on SL buprenorphine/naloxone appears to be on a fee per supervision approach (whereby a community pharmacist dispenses the medication and observes the patient). This reduces

the estimated savings with SC buprenorphine (scenario 1). However, advice from SMC clinical experts confirmed that one large health board has switched to a monthly bundled approach which assumes the NHS incurs a fixed monthly fee for dispensing and supervision.

- The analysis includes differences in hospitalisations between treatments. Given that a cost-minimisation analysis has been submitted, the inclusion of this variable does not seem appropriate as the reason for the reduction in hospitalisations is not clear if equal efficacy is assumed. Scenario analyses which exclude differences in hospitalisations are considered relevant for decision making and are provided in table 2 above.
- In practice SC buprenorphine doses are likely to be tailored to individual patient treatment needs with the flexibility for switches if required. As such there may be some uncertainty surrounding the company's assumption that all patients switch to monthly SC buprenorphine after week 4. Scenario 4 in table 2 above demonstrates the impact of assuming 25% of patients remain on SC buprenorphine weekly injections.
- The company submitted results of a cost-utility analysis as a supplementary analysis. The results were noted and indicated dominance over SL buprenorphine. However, as the company's base case was the cost-minimisation analysis, a full review of the cost-utility analysis was not conducted, and the results are therefore subject to uncertainty.

Whilst SC buprenorphine may have been associated with some additional costs compared to one relevant comparator, the Committee also considered additional factors not captured in the economic analysis. Therefore, despite the uncertainties outlined above, the economic case was considered demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from: Faces & Voices of Recovery UK, Scottish Families Affected by Alcohol and Drugs, the Scottish Drugs Forum Ltd and the Scottish Recovery Consortium. All four organisations are registered charities.
- Faces & Voices of Recovery UK has received 8% pharmaceutical company funding in the past two years, including from the submitting company. Scottish Families Affected by Alcohol and Drugs has received 0.2% pharmaceutical company funding in the past two years, with none from the submitting company. Both the Scottish Drugs Forum Ltd and the Scottish Recovery Consortium have not received any pharmaceutical company funding in the past two years.
- Opioid dependence is a long-lasting condition that can cause major health, social, and economic problems. Complications include overdose and infections (such as HIV and hepatitis C), as well as a vast range of other life-changing physical and mental health conditions. A major part of the recovery process is developing coping strategies to manage

stress and deal with anxiety and cravings. It requires a lot of effort, time, and bravery to confront the issues that have contributed to addiction.

- Opioid replacement therapy (ORT) can reduce the impact of opioid dependence through increasing stability and enabling people to maintain protective factors such as housing, employment and relationships. However, there is a limited range of treatment options and in Scotland the majority of patients are prescribed methadone. The patient groups described the negative impact of supervised daily dispensing on individuals and their families, in terms of restrictions to their daily lives and the stigma of attending the pharmacy so frequently.
- The long-acting nature of Buprenorphine could reduce cravings between doses and allow more sustained management. The delivery method and treatment schedule would remove the stigma and stress of daily ORT dispensing in community pharmacies and would help patients and their families maintain a standard lifestyle of employment, relationships and caring responsibilities. Additionally, the patient groups explained that the new medicine would give patients more control over their treatment and provide the freedom to participate more fully in psychosocial activities for recovery.

Additional information: guidelines and protocols

The Department of Health UK guidelines on clinical management: Drug misuse and dependence were published in July 2017 (minor revisions November 2017). The guideline highlights that drug misuse treatment involves offering a range of psychosocial treatment and support interventions, not just prescribing. Regarding pharmacological treatment, it recommends that methadone and buprenorphine are both effective medicines for maintenance treatment for heroin dependence and that methadone, buprenorphine and lofexidine are all effective in detoxification. Supervision should be available to all patients to support initiation of treatment, and provided for an individually based length of time depending on the patients requirements.⁷

NICE Clinical guideline [CG52]: Drug misuse in over 16s: opioid detoxification, was published in July 2007 (and reviewed January 2019). This guideline recommends that, for patients who are opioid dependent and want to become abstinent, methadone or buprenorphine are first-line treatment options. The chosen option should be based on whether the patient is already receiving maintenance treatment and patient choice, usually the same medication is used. The guideline also notes that lofexidine can be considered in patients with mild/uncertain dependence who have made an informed and clinically appropriate decision not to use methadone or buprenorphine and wish to detoxify within a short time.⁸

NICE Technology appraisal guidance [TA114]: Methadone and buprenorphine for the management of opioid dependence was published in January 2007 (reviewed February 2016). This guideline recommends that flexible dosing of oral methadone and buprenorphine are options for maintenance therapy in the management of opioid dependence, in conjunction with supportive

care. The choice should be made on an individual basis between the patient and clinician taking into account their history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment. If both medicines are suitable, methadone should be prescribed. Supervised daily dispensing should be used for at least 3 months and reduced only when patient is expected to be compliant.⁹

Additional information: comparators

SL buprenorphine and SL buprenorphine/naloxone

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
SC buprenorphine	Maximum dose per week: 32mg with an additional 8mg dose. Maximum dose per month: 128mg with an additional 8mg dose.	Weekly: Up to 2,908 Monthly: Up to 2,876
SL buprenorphine/naloxone	Maximum daily dose: 24mg buprenorphine	Up to 2,971
SL buprenorphine	Maximum daily dose: 24mg	Up to 2,519
Buprenorphine lyophilisates	Maximum daily dose: 18mg	Up to 2,311

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis apart from SC buprenorphine from MIMS online and SL buprenorphine from BNF online on 6 May 2019. Costs do not take any patient access schemes into consideration. Costs for SC buprenorphine would be greater if the additional 8mg dose is administered.

Additional information: budget impact

The company assumed there would be 30,188 patients eligible for treatment in all years. The market share was assumed to be 0.6% (180 patients) in year 1, rising to 4.8% in year 5 (1,437 patients). Discontinuation rates of 9.9% and 51.2% were applied in year 1 and year 5 respectively, resulting in 162 and 701 patients estimated to be treated.

The gross impact on the medicines budget was estimated to be £493k in year 1 rising to £2.1m in year 5. As other medicines were assumed to be displaced the net budget impact was assumed to be £99k year 1 rising to £427k in year 5.

References

1. electronic Medicines Compendium (eMC). Buvidal 64/96/128 mg prolonged-release solution for injection. 2018 [cited 2019 Feb 06]; Available from: <https://www.medicines.org.uk/emc/product/9706/smpc>.
2. electronic Medicines Compendium (eMC). Buvidal 8/16/24/32 mg prolonged-release solution for injection. 2018 [cited 2019 Feb 06]; Available from: <https://www.medicines.org.uk/emc/product/9705/smpc>.
3. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, *et al*. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med*. 2018;178(6):764-73.
4. European Medicines Agency. Buvidal: EPAR Assessment Report. 2018 [cited 2019 Feb 06]; Available from: https://www.ema.europa.eu/documents/assessment-report/buvidal-epar-public-assessment-report_en.pdf.
5. Braeburn Pharmaceuticals, Inc. Clinical Study Report. An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder. Study HS-14-499. 20 June 2017.
6. Frost M, Bailey GL, Lintzeris N, Strang J, Dunlop A, Nunes EV, *et al*. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction*. 2019.
7. Department of Health and Social Care. Drug misuse and dependence: UK guidelines on clinical management. 2017 [cited 2019 Feb 06]; Available from: <https://www.gov.uk/government/publications/drug-misuse-and-dependence-uk-guidelines-on-clinical-management>.
8. NICE. Drug misuse in over 16s: opioid detoxification. 2007 [cited 2019 Feb 06]; Available from: <https://www.nice.org.uk/guidance/cg52>.
9. NICE. Methadone and buprenorphine for the management of opioid dependence. 2007 [cited 2019 Feb 06]; Available from: <https://www.nice.org.uk/guidance/ta114>.

This assessment is based on data submitted by the applicant company up to and including 13 May 2019.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the

individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.