Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2372

buprenorphine 74.2mg implant (Sixmo®)

Accord Healthcare

10 September 2021 *(Issued 5 November 2021)*

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 implant (Sixmo®) is accepted for use within NHSScotland.

Indication under review: for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.

Buprenorphine implant was non-inferior to buprenorphine-naloxone sublingual tablets for controlling illicit drug use in patients transferred from stable daily doses of sublingual buprenorphine up to 8mg.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.[1]

Dosing Information

Each dose consists of four buprenorphine implants (each containing 74.2mg buprenorphine) inserted subcutaneously in the inner side of the upper arm. The implants are intended to be in place and provide a sustained delivery of buprenorphine for six months of treatment. They are removed by the end of the sixth month. Sublingual buprenorphine should be discontinued 12 to 24 hours prior to insertion of buprenorphine implants.

If continued treatment is desired at the end of the first six-month treatment cycle, a new set of four buprenorphine implants may be administered for one additional treatment cycle of six months.

Buprenorphine implants should be used only in patients who are opioid tolerant. Treatment must be under the supervision of a healthcare professional experienced in the management of opioid dependence/addiction. Insertion and removal of the implants must be performed by a physician who is competent in minor surgery and has been trained to conduct the insertion and removal procedure. Patients previously treated with sublingual buprenorphine or sublingual buprenorphine plus naloxone, must be on stable doses between 2 to 8 mg/day for at least 30 days and deemed clinically stable by the treating healthcare professional. Further details on precautions and management are in the summary of product characteristics (SPC).[1]

Product availability date

1 November 2021

Summary of evidence on comparative efficacy

The buprenorphine (Sixmo®) subdermal implant slowly releases buprenorphine, which is an opioid partial agonist and antagonist that binds to the μ (mu) and κ (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties at the μ receptors which, over a prolonged period, minimises opioid cravings.[1]

A double-blind study (PRO-814) recruited adults (18 to 65 years) with a primary diagnosis of opioid dependence who had received at least 24 weeks of sublingual buprenorphine at a stable daily dose ≤8mg for at least 90 days with no evidence of opioid withdrawal or urine sample positive for illicit opioids within the preceding 90 days. Patients were randomised equally to the licensed dose of buprenorphine implant plus sublingual placebo or placebo implant plus sublingual buprenorphine-naloxone at the patient's current stable buprenorphine dose for 24 weeks. The primary outcome was the proportion of patients without evidence of illicit drug use for at least

four out of six months based on urine samples and self-reporting and the primary analysis was non-inferiority at a 20% margin. This was assessed in all randomised patients who received study treatment and had at least one efficacy assessment.[2,3]

For the primary outcome, buprenorphine implant was non-inferior to sublingual buprenorphine-naloxone as the lower limit of the 95% confidence interval (CI) for the proportion difference, 0.088 (95% CI: 0.009 to 0.167), was within the pre-specified margin and subsequent analysis indicated that it was superior for this outcome, as detailed in Table 1 below. There was no hierarchy in the testing of secondary outcomes and no adjustment for multiplicity. There were no differences between the groups for secondary outcomes, including percentage of patients with no illicit drug use each month based on urine samples (≥85% in both) and on self-report (≥79% in both), changes from baseline in measures of craving (100mm visual analogue scales [VAS] for desire to use and need to use) and measures of withdrawal: clinical opiate withdrawal scale (COWS) and subjective opiate withdrawal scale (SOWS).[2,3]

Table 1: Primary and secondary outcome in PRO-814.[2]

	Buprenorphine implant	Buprenorphine-naloxone sublingual	p-value
No illicit drug use in 4 of 6 months*	96% (81/84)	88% (78/89)	p=0.034
Change at EOT in desire to use on VAS	-2.3	-2.8	NS
Change at EOT in need to use on VAS	-2.7	-1.9	NS
Change at EOT in COWS	-0.1	-0.1	NS
Change at EOT in SOWS	-0.6	0.1	NS
Supplemental buprenorphine	18% (15/84)	15% (13/89)	NS

EOT = end of treatment; COWS = clinical opiate withdrawal scale total score (range 0 to 48); SOWS = subjective opiate withdrawal scale total score (range 0 to 64); VAS = 100mm visual analogue scale; NS = not significant * primary outcome.

Two double-blind phase III studies (PRO-805 and PRO-806) recruited adults (18 to 65 years) with a primary diagnosis of opioid dependence who had not received any opioid substitution therapy (buprenorphine or methadone) in the preceding 90 days. Patients were initially titrated with open-label sublingual buprenorphine-naloxone over 10 days in PRO-805 and over 16 days in PRO-806. Those who achieved daily buprenorphine-naloxone doses of 12mg to 16mg for three consecutive days were then randomised to double-blind treatment with buprenorphine implant or placebo, with the PRO-806 group also including an open-label treatment group where patients continued sublingual buprenorphine-naloxone 12mg to 16mg daily. Randomisation was stratified by gender in both studies and also by implant site in PRO-805. The primary outcome was the cumulative distribution function (CDF) of percentage of urine samples negative for illicit opioids during the first 16 weeks in PRO-805 and 24 weeks in PRO-806. The latter study included a co-primary outcome that also included patient self-report of illicit opioid use. These were compared between buprenorphine implant and placebo, with PRO-806 also including a non-inferiority comparison of buprenorphine implant and sublingual buprenorphine-naloxone at a 15% margin. Outcomes were assessed in all randomised patients.[4,5]

In both studies, buprenorphine implant compared with placebo implant significantly improved primary outcomes, percentage of urine samples negative for illicit opioids during the first 16 weeks in PRO-805 and during the first 24 weeks in PRO-806; in the latter study, the co-primary outcome, which included patient self-report of illicit drug use, was consistent with the other primary outcome. Results are detailed in Table 2 below. In both studies, buprenorphine implant compared with placebo implant was associated with higher percentages of urine samples negative for illicit opioids over the 24-week study period, the first 16 weeks and the latter 8 weeks. As secondary outcomes were tested within hierarchies, analyses of COWS, SOWS, VAS of opioid-craving and clinical global impression (CGI) assessed by subject and investigator in PRO-805 were exploratory as they followed non-significant results for total abstinence weeks in the hierarchy, but were in favour of buprenorphine implant versus placebo implant in PRO-806. In the latter study, buprenorphine implant was non-inferior to sublingual buprenorphine-naloxone as the lower limit of the 95% CI for the primary outcome, -11% to 6.2%, was within the pre-specified margin.[2,4-6]

Table 2: Primary and secondary outcomes of PRO-805 and PRO-806.[2,6]

	PRO-805		PRO-806		
	B-implant	**P-implant**	**B-implant**	**P-implant**	**B-sublingual**
Negative urine week 1-24[A,C]	37% (30%)	22% (14%)	31% (20%)	13% (9%)	33% (16%)
Negative urine week 1-16 [A,B]	40% (41%)	28% (21%)	35% (28%)	17% (13%)	36% (19%)
Negative urine week 17-24 [A]	29% (4.4%)	11% (0)	24% (0)	5.9% (0)	28% (6.3%)
LS mean COWS over 24 week	2.3	3.4	2.5	4.5	1.7
LS mean SOWS over 24 week	4.1	6.5	5.3	8.4	2.8
LS mean opioid-craving VAS	9.9	15.8	10.2	21.8	7.1
Supplemental buprenorphine*	59% (64/108)	91% (55/50)	40% (45/114)	-	-

B-implant = buprenorphine implant; P-implant = placebo implant; B-sublingual = buprenorphine-naloxone sublingual; LS = least square; COWS = clinical opiate withdrawal scale total score (range 0 to 48); SOWS = subjective opiate withdrawal scale total score (range 0 to 64); VAS = 100mm visual analogue scale; A = values are cumulative distribution function for percentage of negative urine mean (median); B = primary outcome of PRO-805; C = primary outcome of PRO-806.

* Over weeks 1 to 16 in PRO-805 and weeks 1 to 24 in PRO-806.

Patients who completed PRO-805 and PRO-806 could enter the respective open-label extension studies PRO-807 and PRO-811. In these studies, after removal of implant from the preceding studies, patients underwent a titration period (13 days in PRO-807 and 16 days in PRO-811) with sublingual buprenorphine-naloxone to a daily dose of 12mg to 16mg for at least three consecutive days and then received buprenorphine implant. The studies were primarily designed to assess safety, with efficacy outcomes secondary and descriptive. There were 62 and 85 patients included in PRO-807 and PRO-811, respectively. In PRO-807 the mean percentage of urine samples negative for opioids was 40% over the 24-week study period. Self-reported illicit drug use rate was 42% and 34% at baseline in PRO-807 and PRO-811 and was 55% and 39% at end-of-treatment, respectively. Supplemental buprenorphine-naloxone was given to 42% and 20% of patients in the respective studies. In both studies, withdrawal symptoms and cravings were well controlled at baseline and

remained well controlled throughout the study, as evidenced by the minor fluctuations in mean SOWS, COWS and VAS scale scores throughout the treatment period.[2]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review noted that implant site-related adverse events were an important part of the buprenorphine implant safety profile. These commonly include pain, pruritus, erythema, haematoma, haemorrhage and oedema. They occurred at a slightly higher rate with buprenorphine implant compared with placebo implant, (37% versus 27% using pooled data from the three studies). However, there were no notable differences in the incidence of individual implant site adverse events between treatment groups. Less frequently, there have been reports of implant site infections, implant breakages and implant extrusion and expulsions. Implant site-related adverse events were reported at higher rates in PRO-805 (51% to 58%) than in PRO-806 (26% to 28%) and PRO-814 (14% to 23%) and this may reflect improvements to the administration procedure in the latter two studies, which are employed for commercially available buprenorphine implant.[2]

The non-implant site safety profile was similar between buprenorphine implant and placebo implant/sublingual buprenorphine-naloxone, with no notable differences in non-implant adverse events versus sublingual buprenorphine-naloxone in studies that permitted a direct comparison.[2]

There were safety data from 88 patients who received two cycles of buprenorphine implant in PRO-805 and PRO-806 and their extension studies PRO-807 and PRO-811. These indicated that the safety profile for buprenorphine implant was maintained at one year's exposure.[2]

Buprenorphine implant requires a special procedure for removal and this can create challenges if there is an unexpected change in health status, for example, the patient may need an operation with opioid anaesthesia, become pregnant or require a dose reduction. Buprenorphine can complicate emergency and chronic pain management as it can blunt the pain control of other opioids. In emergency situations caregivers may not be aware that an unconscious patient has buprenorphine implants inserted, which creates a risk of administration of drugs that will interact dangerously with buprenorphine. This is a particular concern during the initial days and weeks after implantation, when buprenorphine levels are relatively high.[2]

Summary of clinical effectiveness issues

Opioid dependence is typically a chronic, relapsing and life-threatening disorder, characterised by compulsive opioid use causing significant mental, physical, and social effects; it can lead to unintentional overdose death. Treatment of opioid dependence involves detoxification followed by long-term abstinence, which may be unachievable, or long-term opioid substitution therapy to reduce morbidity, mortality and offending. Currently available opioid substitution treatments

include methadone and buprenorphine.[2] Guidelines from the UK Department of Health on drug misuse and dependence note that these are both effective at achieving positive outcomes and there is insufficient evidence to justify recommending one drug over the other.[7]

A variety of buprenorphine formulations are licensed for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment, including generic sublingual tablets of buprenorphine alone or in combination with the opioid antagonist, naloxone. There are also proprietary formulations of buprenorphine-naloxone, as Suboxone® sublingual tablet and sublingual film, an oral buprenorphine lyophilisate preparation, Espranor® and a buprenorphine prolonged-release solution for injection, Buvidal®.[8-12] Suboxone® (SMC355/07 and 2316), Espranor® (SMC1245/17), and Buvidal® (SMC2169) have been accepted by SMC for restricted use in patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate.

Buprenorphine implant is the first implant formulation of buprenorphine licensed in the UK. It is indicated for patients on stable daily doses of sublingual buprenorphine up to 8mg.[1]

In patients transferred from stable sublingual buprenorphine (daily dose ≤8mg), buprenorphine implant significantly increased the proportion of patients without evidence of illicit drug use for 4 out of 6 months compared with sublingual buprenorphine-naloxone by about 8%.[2,3] In patients not on opioid substitution therapy who had undergone a short titration to a sublingual buprenorphine daily dose 12mg to 16mg, buprenorphine implant compared with placebo implant significantly improved the percentage of urine samples negative for illicit opioids over the first 16 weeks in one study (PRO-805) and over 24 weeks in another study (PRO-806), with similar results in the latter study for analyses that included patient self-report of illicit drug use. In PRO-806 buprenorphine implant was non-inferior to sublingual buprenorphine-naloxone.[2,4,5] The six-month extensions to PRO-805 and PRO-806 provided overall data up to one year for efficacy of buprenorphine implant in a limited number of patients.[2] The proportion of patients using supplemental buprenorphine-naloxone was lower when they were transferred to buprenorphine implant from sublingual buprenorphine daily doses ≤8mg than doses of 12mg to 16mg: 18% versus 59% and 40% in PRO-814, -805 and -806.[2-5]

There is a lack of long-term data with buprenorphine implant in the indication in clinically stable patients receiving buprenorphine daily dose ≤8mg or data beyond two treatment cycles (12 months). There is no experience of inserting buprenorphine implants into other sites of the arm, sites other than the upper arm or re-insertion into previously-used sites. It is recommended in the SPC that after two treatment cycles most patients should be transitioned back to their previous sublingual buprenorphine dose for continued treatment.[1] This may limit the practical application of a long-term formulation of buprenorphine.

The applicator and the implant technique were changed during clinical development after studies PRO-805 and PRO-807 had been completed. The PRO-806, PRO-811 and PRO-814 studies used the current technique[2] and may provide the best estimate of implant site-related adverse events.

In PRO-805 and PRO-806 patients were not receiving opioid substitution therapy before enrolment and had short titration periods (10 to 16 days) with sublingual buprenorphine-naloxone, which may not reflect practice where the titration period would be longer. The patients in these studies

may not be representative of those likely to be treated with buprenorphine implant within its indication. The population in PRO-814 is more representative as it recruited clinically stable patients who had received sublingual buprenorphine for at least six months and had a daily dose ≤8mg for at least 90 days. In the PRO-805 and PRO-806 studies heroin was the primary opioid of abuse for the majority of patients (62% to 63%), while prescription opioid pain relievers were the primary opioid of abuse for most (74%) patients in PRO-814. The EMA review noted that currently heroin use accounts for the majority, around 80%, of new opioid-related treatment demands in Europe. In the studies, abuse of other psychoactive substances (for example, nicotine and sedatives) was not an exclusion criterion, however, dependence on these was. This may limit the application of study results.[2]

The buprenorphine implant licence limits its use to patients who require buprenorphine daily doses no greater than 8mg. The 2017 Department of Health guideline on drug misuse and dependence notes that doses of buprenorphine between 12mg and 16mg daily are generally recommended. Although some will require lower and higher doses, patients are entitled to be informed what is most likely to be effective. While lower doses than the recommended range may extinguish withdrawal symptoms for a patient, they may still need a higher dose to minimise episodes of craving. Crucially, complete cessation of heroin use may not be achieved until a patient is stabilised within the recommended dose range.[7] Clinical experts consulted by SMC noted that buprenorphine implant may have limited practical application in opioid substitution therapy in practice.

Buprenorphine implant may have limited applications in practice as it is licensed only in patients who are clinically stable on daily doses of sublingual buprenorphine ≤8mg, it can only be used for two treatment cycles (one year), requires minor surgery for insertion/removal and it is associated with implant site adverse events and potential risks if the patient's health status changes unexpectedly, for example if they require emergency surgery. If supplemental buprenorphine is not required, it may allow the patient to have fewer visits to the clinic and pharmacy, which may be beneficial for some patients, in particular for those in rural areas and those keen to avoid the potential stigma of supervision. The implant may be less appropriate for others who require more contact with healthcare professionals to manage their addiction.

The SPC notes that ultrasound and magnetic resonance imaging (MRI) facilities must be available to the clinical site where insertion and removal of buprenorphine implants occurs. Although ultrasound and MRI are not routinely involved in the insertion procedure, they may be required if complications occur or during the removal procedure if the implants are not palpable. Removal of non-palpable implants should be performed under ultrasound guidance or, in case ultrasound is not successful, MRI. Buprenorphine implants are not radiopaque and cannot be seen by X-ray or computed tomography (CT) scan. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.[1] This may have service implications.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating the use of the buprenorphine implant within its full licensed indication. The analysis compared buprenorphine implant with sublingual buprenorphine-naloxone (Suboxone®) and sublingual buprenorphine. Subcutaneous buprenorphine (Buvidal®) was also included as a comparator in the model. Clinical experts broadly agreed these were the relevant comparators.

A cohort-level Markov model was used to represent four distinct health states; "on oral replacement therapy (ORT) and abstinent", "on ORT using illicit opioids", "off ORT and abstinent", "off ORT using illicit opioids", alongside an absorbing health state of Death. The model assumes that all patients enter the model in the "on ORT and abstinent" health state. A one-year time horizon with weekly cycles was used.

Clinical evidence used in the economic evaluation was sourced from study PRO-814.[2] Equal efficacy between buprenorphine implant and subcutaneous buprenorphine and between sublingual buprenorphine and sublingual buprenorphine-naloxone was assumed. The key clinical outcomes were only measured over the first 24 weeks of the treatment period. The submitting company extrapolated the difference in the urine curves of patients abstinent as increasing over the entire time period following the 24-weeks. A scenario was also provided where there was no further separation of the curves. Treatment retention was assumed to be equal across treatment arms and no mortality adjustment was included in the base case.

Health-related quality of life data were not collected in the PRO-814 study. The utility values were therefore obtained from literature. There were few adverse events included in the model, and clinical experts felt this was optimistic as the impact of potential implant-site infections were not captured.

The model included medicine acquisition costs, supplemental medicine costs, medicines administration costs and adverse event costs. Other costs included were health state resource use (HRU) and societal costs. The submitting company assumed that the insertion and removal of the implant would not require any additional training costs to the NHS. For the HRU costs, the submitting company assumed that patients receiving buprenorphine implants would require less frequent clinic visits from week 13. This was one of the key drivers of the costs in the model.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

The base case results are shown below in Table 3 with the PAS. Disaggregated results showed that though acquisition cost is one of the key drivers of the total cost, pharmacy fees for sublingual buprenorphine-naloxone and lower costs for addiction clinic visits for buprenorphine implant were also drivers of this cost.

Table 3: Base case buprenorphine implant vs SL BPN/NX and SL BPN, with PAS

Comparator	ICER Sixmo® versus SL BPN/NX
SL BPN/NX	Sixmo® dominates comparator (cheaper, more effective)
SL BPN	Sixmo® dominates comparator (cheaper, more effective)
SC BPN	£666,059* (Sixmo® is cheaper and less effective)

SL BPN = sublingual buprenorphine, NX= naloxone, SC BPN= subcutaneous buprenorphine ICER= incremental cost-effectiveness ratio
*South-west quadrant ICER

A number of key scenarios are summarised below in Table 4, and an additional combined scenario analysis was requested from the submitting company and presented in Table 5. This was felt to be a plausible, if conservative, scenario by the New Drugs Committee. The key sensitivities included the approach to extrapolation of clean urine curves, frequency of addiction clinic visits, choice of retention curve and the source of hospitalisation costs.

Table 4: Selected scenario analyses results, buprenorphine implant vs. comparators, with PAS

	Structural assumption	Base-case scenario	Other scenarios considered	ICER versus SL BPN/NX	ICER versus SL BPN	ICER versus SC BPN
	Base case			Sixmo® dominates	Sixmo® dominates	£666,059*
1	Time horizon	1 year	2 years	Sixmo® dominates	£18,880	£66,084*
2	Extrapolation of clean urine curve	Maintain trend	Month 6 value carried forward	Sixmo® dominates	£2,853	Sixmo® dominates
3	Choice of retention curve	Equal retention	Estimated from on-top illicit opioid use	£5,688	£15,640	£555,916*
4	Frequency of addiction clinic visits from weeks 13+ for buprenorphine implant	1 visit every 2 months after the initial period	Assumed same as for all comparators (monthly)	£17,905	£28,222	£87,030*
5	Source of hospitalisation costs	DORIS study	PRO-814	Sixmo® dominates	£7,439	£669,471*
6	Proportion of patients with daily pharmacy and increased clinic visits after testing positive for illicit opioid use	100%	50%	Sixmo® dominates	£7,518	£728,845*

SL BPN = sublingual buprenorphine; SL BPN/NX = sublingual buprenorphine-naloxone, SC BPN= subcutaneous buprenorphine
*South-west quadrant ICER

Table 5: Requested combined scenario analyses, with PAS

Parameter/assumption	ICER buprenorphine implant vs. SL BPN/NX)	ICER buprenorphine implant vs. SL BPN
- Source of hospitalisation costs set to PRO-814 - Frequency of addiction clinic visits from weeks 13+ for Sixmo® assumed same as for all comparators (monthly) - Month 6 value carried forward for the extrapolation of clean urine curve	£31,991	£43,644

SL BPN = sublingual buprenorphine; SL BPN/NX = sublingual buprenorphine-naloxone.

Key weaknesses*:*

- The assumption that patients on the buprenorphine implant will have less frequent visits to the addiction clinic is a source of uncertainty and potentially not in line with the licensed indication. As shown in table 4 scenario 4, the ICERs were upwardly sensitive to assuming no differences in clinic visits. The submitting company also provided further sensitivity analysis assuming that there was a 50% reduction in clinic visits for Sixmo®. This gave results of £3,699 and £14,015 versus SL BPN/NX and SL BPN respectively and £376,545 (south-west quadrant) versus SC BPN.
- The extrapolation of the clean urine curve is likely to create an overly optimistic result and the alternative approach using the observed values extrapolated is more appropriate (Table 4, scenario 2).
- The submitting company may have been overly optimistic with regards to implant-site related adverse events in the model with regards to implant-site related adverse events in the model for a patient population of relevance in the Scottish clinical setting. There could be disutilities not included, thus creating an overly optimistic base case.
- The hospitalisation data were sourced from DORIS to reflect the Scottish setting, but the rates sourced from PRO-814 are more appropriate (Table 4, scenario 5).

Despite these limitations, the economic case was demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

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

- We received a patient group submission from Faces & Voices of Recovery UK, which is a registered charity.
- Faces & Voices of Recovery UK has received 8% pharmaceutical company funding in the past two years, with none from the submitting company.
- Patients with opiate addiction can be affected in a variety of different ways. One of the most stark issues and challenges of living with an addictive disorder is learning how to develop new coping and living strategies when trying to get well. It can take months even years to establish new patterns and habits that support recovery. Some of the most pressing challenges is learning to deal with depression, anxiety, cravings and stress.
- Complying with treatment protocols and procedures can take a lot of time and energy. Stigma has a massive effect on treatment and further creates barriers that keep people away from seeking help. Having to attend a pharmacy on a daily basis at a specified time also adds to shame and prevents normal life to take place.
- Buprenorphine implant would give those receiving the treatment a longer time between clinical assessment and more freedom to plan life activities and growth. It would also allow people not to have to face the daily shame and stigma of having to receive medication under such close scrutiny. Learning new coping and living strategies for stress, depression and anxiety could also be easier when the dependency is managed in this way.

Additional information: guidelines and protocols

In 2017 the UK Department of Health updated the 'Drug misuse and dependence UK guidelines on clinical management'. These note that methadone and buprenorphine are both effective at achieving positive outcomes in heroin dependent individuals. Currently, there remains insufficient evidence to justify recommending one drug over the other. The guideline notes that average doses of methadone between 60mg and 120mg daily and of buprenorphine between 12mg and 16mg daily are generally recommended. Although some will require lower and higher doses, patients are entitled to be informed what is most likely to be effective. While lower doses than the recommended range may extinguish withdrawal symptoms for a patient, they may still need a higher dose to minimise episodes of craving. Crucially, complete cessation of heroin use may not be achieved until a patient is stabilised within the recommended dose range.[7]

The National Institute of Health and Clinical Excellence (NICE) Clinical guideline number 52 (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.[13]

In May 2021 the Scottish Government issued Medication Assisted Treatment (MAT) Standards for Scotland, which refer to the use of medication such as opioids, together with any psychological and social support, in the treatment and care of people who experience problems with their drug use. These note that all people are supported to make an informed choice on what medication to use for MAT and the appropriate dose. People will decide which medication they would like to be prescribed and the most suitable dose options after a discussion with their worker about the effects and side-effects. People will be able to change their decision as circumstances change. There should also be a discussion about dispensing arrangements and this should be reviewed regularly.[14]

Additional information: comparators

Other buprenorphine formulations.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per one year course (£)
Buprenorphine implant	One dose every 6 months for one year	2,876

Costs from eMC med data on 19/10/2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 387 patients eligible for treatment with buprenorphine implant in each year. The estimated uptake rate was 5% (19 patients) in year 1 and 20% (77 patients) in year 5.

SMC clinical expert responses indicate the uptake rate is likely to be lower than estimated by the submitting company.

*Other data were also assessed but remain confidential.**

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13. National Institute of Health and Care Excellence. Clinical guideline number 52 (CG52): Drug misuse in over 16s: opioid detoxification, July 2007 (updated January 2019).

14. Scottish Government. Medication Assisted Treatment (MAT) Standards for Scotland, May 2021.

Published 13 December 2021

This assessment is based on data submitted by the applicant company up to and including 13 August 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.