AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Buprenorphine (Sixmo®)
74.2 mg implant

Reference number: 4262

Full submission

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Buprenorphine (Sixmo®▼) 74.2 mg implant

1.0 Key facts

Assessment details	Buprenorphine (Sixmo®▼) for the 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. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Sixmo® is a subcutaneous implant formulation that consists of four implants, each implant (26.5 mm x 2.4 mm) contains 74.2 mg of buprenorphine. Four implants are surgically inserted into the upper arm by a qualified and trained physician.
Current clinical practice	Current clinical practice in treatment of opioid dependence focuses on reduction and discontinuation in illicit drug use. Treatment involves offering a range of psychosocial treatment and support interventions. Pharmacological treatment options for opioid dependence therapy include oral methadone and buprenorphine either as a single agent or in combination with naloxone. Prolonged-release subcutaneous preparation of buprenorphine (Buvidal®) provides a treatment option, which does not require daily supervised use. Sixmo® is the first buprenorphine implant licensed for use in the UK and provides sustained blood levels of buprenorphine for up to six months.
Clinical effectiveness	Results from the key pivotal randomised, double-blind phase III study showed Sixmo® was non-inferior to sublingual buprenorphine/naloxone in reducing illicit opioid use over the 6-month treatment period. No difference was seen for the secondary endpoints, which included opioid cravings and retention rates for treatment. The study was limited to one treatment cycle of 6 months and long-term efficacy is unclear. Supportive data come from two additional phase III studies that compared Sixmo® with placebo; one included an open-label treatment arm for sublingual buprenorphine/naloxone. In both studies, the percentage of negative urine tests for opioids was

	statistically significant in favour of Sixmo® although the number of urine tests that were negative for opioid use decreased towards the end of the treatment period. In all three studies, patients could take supplemental sublingual buprenorphine if needed. Safety data related to implant and route of administration are limited to two treatment cycles of six months. No clinical studies directly compare Sixmo® with Buvidal®; the company's literature search did not identify any studies suitable for indirect treatment comparisons or meta-analysis.
Cost-effectiveness	A cost-utility analysis compares buprenorphine (Sixmo®) subcutaneous implant with sublingual buprenorphine/naloxone, and subcutaneous buprenorphine (Buvidal®), as a 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. The company base case suggests that Sixmo®, which has an associated Wales Patient Access Scheme discount, is the dominant treatment option when compared with sublingual buprenorphine/naloxone. The base case also suggests an incremental cost-effectiveness ratio of [commercial in confidence figure removed] saved per quality-adjusted life-year (QALY) forgone when compared with subcutaneous buprenorphine. When compared with sublingual buprenorphine/naloxone AWTTC considers it plausible that Sixmo® is the dominant treatment option, or that the incremental cost-effectiveness ratio is < £20,000 per QALY gained. When compared with subcutaneous buprenorphine AWTTC considers a positive net monetary benefit to be plausible. The model is characterised by both structural and parameter uncertainties. However, extensive sensitivity and scenario analyses have been conducted to test the impact of these.
Budget impact	The company estimates that 6 patients are likely to receive treatment with Sixmo® in Wales in Year 1, increasing to 22 in Year 5. The company base case suggests an additional cost of [commercial in

	confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings valued at £10,482 in Year 1, increasing to £41,929 in Year 5, resulting predominantly from a reduction in administration costs and the number of addiction clinic visits. It is questionable whether the predicted resource savings attributed to reduced clinic visits will be realised, given that the Summary of Product Characteristics for Sixmo® recommends a minimum frequency of once-monthly continued counselling and psychological support.

This assessment report is based on evidence submitted by Accord Healthcare and an evidence search conducted by AWTTC on 12 July 2021[1].

2.0 Background

2.1 Condition and clinical practice

Opioid dependence is a chronic and relapsing condition that involves the compulsive use of prescribed opioid medicines or illicitly obtained opioids such as heroin[2]. Opioid dependence is an important public health problem and may cause significant mental, physical and social distress as well as transmission of blood-borne infections such as HIV and hepatitis B or C, unintentional overdose, criminal activity and incarceration[2,3]. Current clinical practice focuses on reduction in illicit drug use and complete abstinence from illicit opioids is considered an ideal outcome[2,4]. Treatment involves either long-term opioid substitution or detoxification along with psychological and behavioural assistance[2].

The most commonly used opioid substitution treatments are oral methadone and buprenorphine either as a single agent or in combination with naloxone[3]. The UK guidelines on clinical management of drug misuse and dependence do not recommend one drug over the other and advise buprenorphine is an effective medicine for maintenance opioid treatment, particularly when taken within the optimal dose range, 12 mg to 16 mg daily[4]. The daily doses should be taken under the direct supervision of a professional to support induction on to opioid substitution therapy and allow monitoring of progress, which is relaxed only when appropriate to an individual's needs and risks[5].

In 2019, the All Wales Medicines Strategy Group (AWMSG) recommended the use of subcutaneous prolonged-release preparation of buprenorphine (Buvidal®)[6]. The medicine removes the need for daily dosing and provides patients with sustained concentrations of buprenorphine over a period of weeks.

2.2 Medicine

Buprenorphine is a semi-synthetic opioid with partial agonist and antagonist properties and binds to the mu and kappa receptors of the brain[7]. In opioid maintenance treatment its activity is attributed to its slowly reversible properties at the

mu receptors which, over a prolonged period, minimises opioid cravings[2]. Because of its slow onset of action, patients are less likely to experience sedation or euphoria when taking an appropriate dose[2].

Buprenorphine 74.2 mg implant (Sixmo®) was granted marketing authorisation by the European Medicines Agency in June 2019[3]. It is licensed for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine (SL BPN), within a framework of medical, social and psychological treatment[3].

Sixmo® is a long-acting therapy; it is given as an implant surgically placed under the skin that continuously releases buprenorphine into the body for six months[8]. It is suitable only for patients who are opioid tolerant, and have been previously treated with SL BPN or sublingual buprenorphine with naloxone (SL BPN/NX). Patients must be on stable doses between 2 mg/day to 8 mg/day for at least 30 days and deemed clinically stable by the healthcare professional treating them[8].

Sixmo® implants must be inserted and removed by a doctor who is competent in minor surgery and has been trained to insert and remove the implants[8]. Under local anaesthesia, four implants are placed in the inner side of a patient's upper arm. These are kept in place for 6 months and removed by the end of the sixth month. During the 6-month treatment period, if some patients feel they need supplemental dosing a doctor should evaluate and consider giving them additional SL BPN. After the first 6-month treatment, if a person needs continued treatment with buprenorphine a new set of 4 implants may be placed in the person's other arm, to give one additional 6-month treatment. At the end of the second 6-month treatment, the implants are removed and most patients who need continued treatment go back to taking their previous SL BPN dose[8]. There is no experience of re-implantation beyond 12 months[8].

2.3 Comparators

The comparator(s) included in the company's submission[1] are:

- sublingual buprenorphine (SL BPN);
- sublingual buprenorphine/naloxone (Suboxone®) (SL BPN/NX);
- extended-release or depot subcutaneous buprenorphine (Buvidal®) (SC BPN); and
- buprenorphine oral lyophilisate (Espranor®).

2.4 Guidance and related advice

- UK Government Department of Health (2017) Drug misuse and dependence: UK guidelines on clinical management[4]
- National Institute for Health and Care Excellence (NICE) (2007) TA 114: Methadone and buprenorphine for the management of opioid dependence[9]
- NICE (2007) Clinical guideline CG52: Drug misuse in over 16s: opioid detoxification[5]

The All Wales Medicines Strategy Group (AWMSG) recommended with restrictions the use of buprenorphine/naloxone (Suboxone®) sublingual tablets in July 2008 and sublingual film in April 2021[10,11]. The All Wales Medicines Strategy Group (AWMSG) recommended the use of buprenorphine (Buvidal®) in September 2019[6].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, buprenorphine (Sixmo®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The company's submission includes evidence from three phase III studies: PRO-814, PRO-805 and PRO-806[1]. PRO-814 is the key pivotal study, comparing Sixmo® with SL BPN/NX in adults. PRO-805 and PRO-806 provide supportive data on efficacy and pharmacokinetics. The company conducted a literature review but did not find evidence that would allow an indirect treatment comparison of Sixmo® with Buvidal® or Espranor®. Studies of the comparator treatments were conducted in different populations to that indicated for Sixmo®.

3.1 Study PRO-814[12,13]

This 24-week, double-blind, double-dummy study, conducted at 21 office-based outpatient treatment sites in the USA, enrolled 177 adults (mean age 39 years) who were clinically stable receiving sublingual buprenorphine (SL BPN) or sublingual buprenorphine/naloxone (SL BPN/NX). To be eligible to take part in the study, patients had to have received SL BPN for at least 24 weeks as an outpatient at a stable dose of 8 mg/day or less. In addition, patients had to show no evidence of opioid withdrawal or illicit opioid-positive urine samples for at least 90 days before starting the study. Most patients (74%) were addicted to prescription opioid painkillers; 21% were addicted to heroin.

Patients were randomised 1:1 to receive either:

- daily SL BPN/NX tablets (continuing at the same dose they took before starting the study) plus 4 subdermal implants of placebo (n = 87); or
- daily sublingual placebo tablets plus 4 Sixmo® subdermal implants of 80 mg buprenorphine (n = 90).

Supplemental SL BPN/NX to treat additional symptoms of opioid dependence was allowed at the discretion of the investigator without any limitations. All implants were removed after 24 weeks (6 months).

The study's primary endpoint was the difference in the proportion of responders between each treatment group. Responders were defined as patients with at least 4 of 6 months without evidence of illicit opioid use (based on urine test results and self-reporting). Urine samples and self-report assessments were taken at Week 1 and then at 4-week intervals, with an additional 4 urine samples collected at random intervals. The study tested non-inferiority of Sixmo® relative to SL BPN/NX based on the primary outcome with non-inferiority established for a lower bound of the 95% confidence interval (CI) > −0.20.

The results (see Table 1) showed the proportion of responders was 87.6% in the group that received SL BPN/NX and placebo implants, and 96.4% in the group that received sublingual placebo and Sixmo®. The difference of 8.8% (one sided 97.5% CI 0.009 to ∞) established non-inferiority of Sixmo® over SL BPN/NX ($p < 0.001$), and superiority of Sixmo® over SL BPN/NX ($p = 0.034$).

Secondary outcomes included the cumulative distribution function of the percentage of negative illicit opioid urine results at 6 months in each treatment group; control of opioid cravings; supplemental SL BPN use; and treatment retention. At 6 months, the proportion of patients with no urine illicit opioid use for the cumulative abstinence was 85.7% for Sixmo® and 71.9% for SL BPN/NX (hazard ratio, 13.8; 95% CI, 0.018 to 0.258; p = 0.03). Clinical opioid withdrawal scores and subjective opioid withdrawal scores were low for patients in both treatment groups, with no statistically significant changes over the treatment period.

The numbers of patients who received supplemental medication during the study were 15 (18%) in the Sixmo® group and 13 (15%) in the SL BPN/NX group. In both groups, most patients were prescribed small doses (2 mg/day) on 4 occasions or fewer during the study. Retention in treatment was high in both treatment groups.

Table 1. Results from studies[12,14,15]

Study PRO-814	**Sixmo®**	**SL BPN/NX**	**p value**
Patients (n)	87	90	
Primary endpoint: responders (patients with at least 4 of 6 months without illicit opioid use)	81/84* (96.4%)	78/89** (87.6%)	<0.001 (for non-inferiority)
Opioid abstinence	72/84 (85.7%)	64/89 (71.9%)	0.03
Patients completing 24-week study	81/87 (93%)	84/90 (93%)	
Study PRO-805	**Sixmo®**	**Placebo implant**	**p value**
Patients (n)	108	55	
Primary endpoint: urine samples negative for illicit opioids for Week 1 to 16	40.4%	28.3%	0.04
Patients completing 24-week study	71/108 (65.7%)	17/55 (30.9%)	<0.001
Study PRO-806	**Sixmo®**	**Placebo implant**	**p value**
Patients (n)	114	54	
Primary endpoint: urine samples negative for illicit opioids for Week 1 to 24	31.2%	13.4%	<0.0001
Patients completing 24-week study	73/114 (64%)	14/54 (26%)	0.0002
Sixmo®: buprenorphine implant, SL BPN/NX: sublingual buprenorphine/naloxone *87 patients in PRO-814 were randomised to receive buprenorphine implants but three patients did not have post-baseline assessments. **90 patients in PRO-814 were randomised to receive sublingual buprenorphine/naloxone but one patient did not receive the study medication.			

3.2 Studies PRO-805 and PRO-806[14,15]

PRO-805 and PRO-806 are two randomised, double-blind phase III studies that compared Sixmo® against placebo implants for 24 weeks in adult patients with opioid dependence who had not previously received buprenorphine[8]. These studies included more patients who were addicted to heroin than in study PRO-814: proportions in the treatment groups ranged from 52% to 67%. Study PRO-806

included an open-label comparator treatment arm with patients taking 12–16 mg/day SL BPN/NX. In both studies, patients in all groups were allowed to use supplemental SL BPN if needed[8].

Results (see Table 1) for both studies showed a statistically significant difference in favour of Sixmo® versus SL BPN/NX in the primary endpoint for urine samples testing negative for illicit opioid use during the studies[14,15]. Significantly more patients completed 24 weeks of treatment with Sixmo® than completed placebo treatment[8]. In both studies the numbers of urine tests that were negative for opioid use decreased towards the end of the treatment period, showing a reduction in efficacy of Sixmo® over time[2]. In study PRO-806 the proportion of urine samples testing negative for illicit opioids for Sixmo® and the SL BPN/NX group were 31.2% versus 33.5%. The lower bound of the 95% CI for the mean difference in the results of −10.7% was greater than the pre-specified margin of −15% indicating that Sixmo® was non-inferior to SL BPN/NX[8].

The proportion of Sixmo® patients who received supplemental SL BPN/NX was 59% and 40% in studies PRO-805 and PRO-806, respectively[14,15]. A self-rated clinical global improvement tool measured quality of life for the patients in studies PRO-805 and PRO-806. Reductions in illicit drug use were 14.2% and 17.8%, respectively, over 6 months. However, there was no direct correlation between improvement in quality of life and illicit drug use[2].

3.3 Safety information

The safety of Sixmo® has been evaluated primarily based on pooled data from the double-blind studies PRO-814, PRO-805 and PRO-806, plus supportive data from two extension studies[2]. The safety profile of Sixmo® is in line with the established safety data for buprenorphine except for implant site reactions[2]. Serious adverse events related to buprenorphine use are uncommon and include severe respiratory failure, hepatitis and allergic reactions. Common adverse effects most frequently reported for buprenorphine use include headaches, constipation, nausea and insomnia[8] and rates were similar in both the Sixmo® and SL BPN/NX groups.

The safety profile of Sixmo® is dominated by adverse events related to the site of the implant, reported in around 33% of patients in the double-blind studies[2]. These were generally mild to moderate in severity and rarely led to discontinuation of Sixmo®. The most common adverse reactions due to implant insertion and removal were pain, redness, haematoma, bleeding, rash and swelling and were slightly higher than those seen in patients who had placebo implants and SL BPN/NX. The Committee for Medicinal Products for Human Use (CHMP) noted there were six documented cases of clinically significant implant breakage post marketing, implant migration and difficulty removing the implants. As part of the additional risk minimisation measures, the company will provide practical insertion and removal training for healthcare professionals to reduce the risk of site adverse reactions[2].

There are no long-term data available in relation to the repeat insertion of Sixmo® implants beyond two treatment cycles of six months (one year treatment in total)[2]. The planned PRO-816 study, which will enrol 1300 patients, will examine safety of Sixmo® further[2].

3.4 Ongoing studies

A prospective, observational safety study is planned to evaluate the rate of breakage of Sixmo® implants reported during a treatment period and whether breakage is clinically significant. The study aims to enrol 740 patients with opioid addiction who meet the criteria for treatment with Sixmo®[1].

3.5 AWTTC critique

- Sixmo® is the first buprenorphine implant licensed for use in the UK and would provide an additional treatment option for patients with opioid dependence. It is a long-acting therapy designed to provide continuous, non-fluctuating, blood levels of buprenorphine for up to two six monthly cycles.
- The PRO-814 pivotal study showed non-inferiority of Sixmo® to sublingual buprenorphine/naloxone in reducing patients' use of illicit opioids. There is no indirect treatment comparison with Buvidal®.
- Sixmo® use is limited to a subpopulation of patients with opioid dependence who are clinically stable on a dose of 8 mg or less of sublingual buprenorphine. Welsh experts advised AWTTC that most patients are usually treated on higher doses of buprenorphine. Sixmo® may be an option in patients who are clinically stable on low doses of buprenorphine and it may reduce inconvenience for individuals, enabling less disruption of employment, education and/or life.
- The applicant company suggests Sixmo® could potentially address shortcomings associated with daily self-administration of buprenorphine tablets, such as poor compliance, adherence, misuse and diversion[1]. However, Sixmo® is a fixed dose implant for a six or twelve month duration, it is not as flexible as oral dosing regimens and therefore will not meet the needs of patients when dose changes are required. The CHMP and Welsh clinical experts recommend careful patient selection and this may limit its use.
- Sixmo® must be administered by a healthcare professional who is competent in minor surgery and has had training to insert, and remove, the implants. The applicant company will provide, and pay for, their training although the healthcare professional will need access to specialised equipment where implants are non-palpable e.g. an ultrasound and MRI facilities which may not be available in outpatient addiction clinics and GP surgeries. This may have service implications.
- Reduced illicit opioid use in patients receiving Sixmo® versus placebo implants in studies PRO-805 and PRO-806 did not correlate with improvement in their quality of life.
- The evidence for the clinical efficacy of Sixmo® relies mainly on the pivotal study (PRO-814), in which 75% of patients were addicted to prescription opioid medicines. However, in Wales, most patients with opioid dependence are addicted to heroin.
- Studies PRO-805 and PRO-806 showed a significant proportion of patients needed supplemental SL BPN during Sixmo® treatment. These patients will need to attend a clinic to receive SL BPN, reducing the convenience of Sixmo®.
- Insertion and removal of Sixmo® is associated with rare but serious complications that include implant migration, protrusion, expulsion, and nerve damage resulting from the procedure[8].
- Following a maximum of one year of treatment, most patients who receive Sixmo® should be transitioned back to their previous sublingual buprenorphine

dose for continued treatment[8]. Opioid dependence is a chronic, relapsing condition; therefore, the long-term benefits of Sixmo® are unclear.

4.0 Cost-effectiveness

4.1 Context

The company's submission includes a cost-utility analysis comparing buprenorphine subcutaneous implant (Sixmo®) with sublingual buprenorphine/naloxone (SL BPN/NX), and subcutaneous buprenorphine (Buvidal®) (SC BPN), as a substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine (SL BPN), within a framework of medical, social and psychological treatment.

The cost-utility analysis takes the form of a Markov cohort model, comprising weekly cycles. The model adopts a 2-year time horizon and an NHS Wales/Personal and Social Services perspective. The submission incorporates a Wales Patient Access Scheme (WPAS) discount for Sixmo®. Costs and outcomes are discounted at 3.5%. The model is characterised by five health states: on opioid replacement therapy (ORT) abstinent; off ORT abstinent; on ORT using illicit opioids; off ORT using elicit opioids; and death. All patients enter the model in the 'on ORT abstinent' health state. Once patients transition to either one of the 'off ORT' states, they cannot transition back to an 'on ORT' state. Patients can transition to death from any health state.

Transition probabilities are extrapolated from the efficacy data collected in the pivotal PRO-814 study; a 24-week head-to-head comparison of Sixmo® vs SL BPN/NX[12]. Due to lack of available data in the literature for the targeted patient population, equal efficacy for abstinence is assumed in the model between Sixmo® and SC BPN. Retention in treatment is assumed to be equal for all treatments, based on the observed data from the SL BPN/NX arm of PRO-814, given the lack of a statistically significant difference in the study[12]. Every 6 months patients can switch treatment from Sixmo® to SL BPN/NX. It is assumed that all patients testing positive for illicit opioid use at each six-month interval switch to SL BPN/NX because Sixmo® is only indicated for clinically stable patients. The proportion of abstinent patients who go on to receive subsequent lines of treatment with Sixmo® is based on Welsh clinical expert opinion, given that patients in the treatment arm of the pivotal study received only one six-month treatment cycle of Sixmo®. It is assumed that 20% of patients will switch to SL BPN after 6 months. 80% of those who remain on treatment in the second six-month cycle will switch after 1 year; the remaining 20% of patients are modelled to commence a third treatment cycle. 75% of those remaining on treatment at the end of the third cycle switch after that cycle (i.e. after 18 months) and no patients continue treatment beyond 2 years. The model does not adjust for mortality, but it does estimate the number of patients with moderate-severe implant site or inject site adverse events (AEs), for Sixmo® and SC BPN respectively, based on study incidence data[12,16].

The model incorporates medicine acquisition, administration costs, and pharmacy controlled-drug related fees, including those associated with supplemental treatment for breakthrough symptoms. List prices for the comparator medicines are sourced from the British National Formulary and NHS drug tariff[17,18]. The mean daily dose for SL BPN/NX is informed by the pivotal study[12]. Following Welsh clinical expert advice,

the base case applies the monthly formulation cost for SC BPN every 4 weeks to reflect the monthly dosing protocol, rather than the weekly formulation at each cycle (which is alternatively explored in scenario analyses). Supplemental treatment frequency and dosing, with sublingual formulation, is guided by the pivotal study for patients receiving Sixmo® or SL BPN/NX and the literature for those receiving SC BPN[19].

In terms of administration, it is assumed that GPs undertake Sixmo® implantation and removal during a 30 minute appointment; with unit costs extracted from PSSRU[20]. In instances where the implant is not palpable, an ultrasound scan is used to locate them. Probability of this event is guided by the pivotal study, and unit cost is taken from NHS Reference Costs[21]. For SC BPN it is assumed that injections are administered by a specialist nurse during routine visits to substance abuse clinics, with unit costs taken from PSSRU[21]. The same dispensing and controlled-drug fees are assumed for Sixmo® and SC BPN. Lower controlled drug fees but additional supervised consumption fees are applied for SL BPN/NX. These pharmacy controlled-drug related costs are guided by information provided by Welsh clinical experts.

Health state resource use comprises monitoring costs, and primary and secondary care usage associated with treatment of opioid dependency, including additional clinic and GP visits, urine testing, outpatient and community treatment visits, A&E visits and hospitalisations. Frequency of urine testing and addiction clinic visits were elicited from two Welsh clinicians working in substance abuse clinics. Accordingly, it is assumed that patients receiving Sixmo® require fewer addiction clinic visits to assess patients' progress after "Week 12", (equal addiction clinic visits are explored in scenario analysis). Other resource use is guided by an English economic analysis underpinned by the National Treatment Outcome Research Study (NTORS) study[22], and costed using standard sources[20,21]. Costs associated with adverse events are not explicitly modelled. It is assumed that adverse events will be dealt with when patients attend substance abuse clinics, therefore the associated resource use is already captured in health state costs.

Health outcomes are accrued in each of the health states, predominantly informed by the literature[22]. Values are directly applied to all health states incorporated within the economic model, aside from the 'off ORT abstinent' health state. Given the lack of a value for this health state in the literature, it is assumed to be equal to that of the 'on ORT abstinent' state. In keeping with the Connock study data[22], the model differentiates between injectors and non-injectors; health-state utilities are lower in patients injecting illicit opioids compared to those who are not injecting. The model assumes that 60% of patients are injectors at baseline, in keeping with data from England, because no data were identified for Wales[23]. Utility decrements for implant-site reaction (Sixmo® arm) and injection-site reaction (SC BPN arm) are also included in the model. The disutility for SC BPN was sourced from a study conducted in Scotland that reported the utilities and disutilities for attributes of injectable treatments for type 2 diabetes[24]. Because no disutility values were identified in the literature for implanted treatments, the model applies the same disutility value for implant-site adverse events occurring in Sixmo® patients.

Deterministic and probabilistic sensitivity analyses test the influence of the uncertainty of individual parameters on the model results. The parameters tested, amongst others, include: proportion of patients using opioids at 24 weeks, addiction

clinic visits, utility values, proportion of patients receiving supplemental treatment, and discontinuation of treatment.

Scenario analyses also explore alternative assumptions and/or data sources, including: time horizon, treatment retention, frequency of addiction clinic visits, the proportion of patients incurring bundled pharmacy fees, switching to SL BPN/NX at the end of each six-month period, mortality, hospitalisation rates, and the inclusion of societal costs. Sublingual buprenorphine (SL BPN) and Espranor® are additionally explored as alternative comparators.

4.2 Results

The results of the base case are detailed in Table 2. When compared with SL BPN/NX Sixmo® dominates (i.e. is less costly and more effective). The main cost differences can be attributed to lower pharmacy controlled-drug related costs and addiction clinic visits. The incremental QALY gains are predominantly driven by a higher probability of patients receiving Sixmo® remaining in the 'on ORT abstinent' state over time.

When compared with SC BPN, the point estimate for the ICER falls within the south-west quadrant of the cost-effectiveness plane (i.e. Sixmo® is less costly and less effective than SC BPN), producing an ICER of [commercial in confidence figure removed] saved per QALY forgone. In the south-west quadrant, an ICER > £20,000 saved per QALY forgone can deliver a net health benefit at a population level and provide additional treatment options for patients. The company identifies that treatment with Sixmo® is associated with a net monetary benefit of [commercial in confidence figure removed], when a QALY is valued at £20,000. The main cost differences can be attributed to lower medicine acquisition costs. The incremental QALY losses are predominantly driven by fewer patients remaining in the on ORT abstinent state over time, as a result of switching to SL BPN N/X.

Table 2. Results of the base case analysis

	Sixmo®	Comparator treatment	Difference	NMB valuing a QALY at £20,000
Sixmo® versus SL BPN/NX				
Medicine acquisition costs	¶¶	£1,291	¶¶	¶¶
Medicine administration costs	£429	£0	**£429**	
Pharmacy controlled-drug related fees	£929	£1,849	**−£920**	
Addiction clinic visits	£4,869	£6,459	**−£1,590**	
Other costs	£2,549	£2,591	**−£42**	
Total costs	¶¶	£12,190	¶¶	
Total QALYs	1.5377	1.4848	**0.0529**	
ICER (£/QALY)	**Sixmo® dominates**			
Sixmo® versus SC BPN				
Medicine acquisition costs	¶¶	£5,100	¶¶	¶¶
Medicine administration costs	£429	£192	**£236**	
Pharmacy controlled-drug related fees	£929	£151	**£778**	
Addiction clinic visits	£4,869	£4,832	**£37**	
Other costs	£2,549	£2,535	**£14**	
Total costs	¶¶	£12,810	¶¶	
Total QALYs	1.5377	1.5555	**−0.0178**	
ICER (£/QALY)	¶¶*			

ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life-year; SC BPN: subcutaneous buprenorphine; SL BPN/NX: sublingual buprenorphine/naloxone
¶¶: commercial in confidence figure removed
*point estimate in south west quadrant of the cost-effectiveness plane. In the south-west quadrant ICERs ≥ £20,000 – £30,000 per QALY forgone can deliver a net health benefit at a population level and provide additional treatment options for patients – these medicines can therefore be considered a worthwhile treatment option. Note: ICERs may not compute due to rounding.

The results of the univariate sensitivity analysis reveal that the ICER for the Sixmo® versus SL BPN/NX comparison is relatively stable, being most sensitive to: the proportion of patients using opioids at 24 weeks for both treatment arms; frequency of addiction clinic visits and associated unit cost; and the utility values used for 'On ORT abstinent' and 'On ORT using illicit opioids and injecting'. All ICERs produced in the univariate analyses produced ICERs below £20,000 per QALY gained.

In the comparison between Sixmo® and SC BPN the ICER is most sensitive to the proportion of patients using opioids at 24 weeks for both treatment arms and the frequency of addiction clinic visits. All analyses conducted produced a positive net monetary benefit associated with the treatment of Sixmo®.

Probabilistic sensitivity analyses indicate that Sixmo® has a 93% and 89% probability of being the most cost-effective treatment option at a threshold of £20,000 and £30,000 per QALY gained, respectively.

Table 3. Results of scenario and sensitivity analyses

Scenario	ICER or NMB valuing a QALY at £20,000	Plausibility
1-year time horizon a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) Sixmo® dominant** **b) ¶¶* NMB ¶¶**	The EPAR for Sixmo® identifies limited experience of a second treatment cycle, and no experience of reimplantation beyond 12 months[2]. This time horizon therefore better reflects the current evidence base and offers a plausible alternative to the base case.
Frequency of addiction clinic visits from week 13+ for Sixmo® a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) Sixmo® dominant** **b) ¶¶* NMB ¶¶**	This scenario explores the impact of assuming the same frequency of addiction clinic visits as the comparators. If addiction clinic visits are considered to be an important component of the wider framework of medical, social and psychological support, this scenario may offer a plausible alternative to the base case.
Alternative comparators a) Sixmo® vs SL BPN b) Sixmo® vs Espranor®	**a) Sixmo® dominant** **b) Sixmo® dominant**	This scenario explores alternative comparators. However, these comparisons are limited to medicine acquisition cost adjustments only. All other inputs are assumed equal to SL BPN/NX.
Treatment retention curve estimated from on-top illicit opioid use data collected in a retrospective chart review study[25]. a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) ¶¶** **b) ¶¶* NMB ¶¶**	The company suggests that retention rates observed within clinical studies may not be representative of those in clinical practice. This scenario uses real world data from the USA to explore the relationship between opioid use when on ORT and retention rates. Using these data in the model, more patients transition to the off-ORT health states as a result of lower retention overall. This scenario provides a useful, more conservative estimate of retention than the base case. However, these data may not be representative of the target patient population, in terms of clinical stability or context.

Scenario	ICER or NMB valuing a QALY at £20,000	Plausibility
Hospitalisation costs sourced from pivotal study: PRO-814 a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) Sixmo® dominant** **b) ¶¶* NMB ¶¶**	This scenario uses data from the pivotal study for hospitalisation. While it offers insight into hospitalisation in the targeted population, it includes the costs incurred as a result of a child consuming SL BPN during the pivotal study in the comparator arm costs.
Proportion of patients with daily pharmacy and increased clinic visits after testing positive for illicit opioid use reduced to 50% (100% in base case) a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) £ Sixmo® dominant** **b) ¶¶* NMB ¶¶**	In this scenario the base case assumption that all patients using on-top opioids revert back to daily pickup and supervised consumption of SL BPN is relaxed.
Inclusion of societal costs: a) Sixmo® vs SL BPN/NX b) Sixmo® vs SC BPN	**a) Sixmo® dominant** **b) ¶¶* NMB ¶¶**	This scenario provides a useful insight into the effects of the inclusion of societal costs.
EPAR: European public assessment report; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; ORT: opioid replacement therapy; QALY: quality-adjusted life-year; SC BPN: subcutaneous buprenorphine; SL BPN/NX: sublingual buprenorphine/naloxone ¶¶: commercial in confidence figure removed *point estimate in south-west quadrant of the cost-effectiveness plane. In the south-west quadrant ICERs ≥ £20,000 - £30,000 per QALY forgone can deliver a net health benefit at a population level and provide additional treatment options for patients – these medicines can therefore be considered a worthwhile treatment option.		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Justifications are provided for the assumptions applied in the model.
- Extensive sensitivity and scenario analyses have been conducted.
- The model does not facilitate a patient relapsing and later restarting ORT. It is uncertain whether this is a realistic structural assumption in the model. The company identify a lack of longitudinal follow-up data for patients who drop out of treatment as the rationale for not including this feature.

- The SPC for Sixmo® identifies a lack of evidence for any more than two cycles of treatment[2]. The two-year time horizon therefore increases the uncertainty in the model associated with longer-term cost-effectiveness.
- No indirect comparison was conducted to compare Sixmo® to SC BPN and thus the model assumes that SC BPN has an equal effect on retention and opioid misuse as Sixmo®. There are no data to support this assumption. However, AWTTC-sought expert opinion suggests this is a plausible assumption.
- Data collected in Week 24 of the pivotal study are extrapolated as a constant risk to inform longer term efficacy. This introduces uncertainty in efficacy estimates. However, the additional analyses to explore alternative waning assumptions have been undertaken. The results of these additional scenarios do not alter cost-effectiveness conclusions.
- The health state utility values used in the model are taken from a study published in 2007. They were derived using a vignette approach where health state descriptions (vignettes) were valued by members of the UK public through standard gamble (SG) methods. The use of UK values is in keeping with good practice. However, preferences can change over time. Therefore, it is uncertain whether the values used are reflective of current values.
- The proportion of patients who continue treatment with Sixmo® after the first treatment cycle is based on expert opinion only, which introduces uncertainty. However, this uncertainty is explored through scenario analyses. The company conducted additional analyses upon request to explore the impact of a more conservative assumption of all patients reverting back to SL BPN/NX after 6 and 12 months. This did not alter the cost-effectiveness conclusions.
- Health state resource use has been estimated by two Welsh clinical experts in combination with reference to the literature. Although relatively recent unit costs have been applied, it is uncertain whether the standard of care and resource have remained unchanged since the collection of the data used in the NTORs study[22]. This introduces uncertainty in the health state resource use estimates.
- The assumption of 60% of patients being injectors at baseline is an overestimate. The company have provided more recent figures indicating the proportion is closer to 23%[23]. Additional analyses reveal that correction of this parameter does not alter cost-effectiveness conclusions.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of Sixmo® versus sublingual or subcutaneous buprenorphine as substitution treatment for opioid dependence.

5.0 Budget impact

5.1 Context and methods

The company estimates that there will be 110 eligible patients in Years 1 to 5. This estimate is guided by Welsh statistics, which identify that 672 patients were initiated on buprenorphine between 2018 and 2019[26]. This prevalence is applied in Year 1 and is assumed to remain constant over subsequent years. A mortality rate of 0.43% is informed by a systematic review and meta-analysis focused on mortality risk during and after ORT[27]. An assumption that approximately 16% of patients receiving SL

BPN are clinically stable and receiving between 2–8 mg is guided by Welsh clinical expert opinion and Scottish prescribing data. An assumed market share of 5% in Year 1, increasing to 20% in Year 5 is further applied to estimate the number of people likely to be prescribed Sixmo® in Wales for the indication covered in the submission. The company provides a breakdown of how comparator medicines are likely to be displaced as a result. Current market shares for the comparators are guided by Welsh prescribing data. The WPAS discount is applied to Sixmo®. All other medicines acquisition costs reflect list prices. No sensitivity analyses have been performed.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing Sixmo® would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of SL BPN/NX, SL BPN, and SC BPN.

Table 4. Company-reported costs associated with use of Sixmo® as substitution treatment for opioid dependence in the indicated population

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	110	110	110	110	110
Uptake of new medicine (%)	5%	8%	10%	15%	20%
Number of patients receiving new medicine allowing for discontinuations	6	8	11	17	22
Medicine acquisition costs in a market without new medicine	£55,990	£55,990	£55,990	£55,990	£55,990
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£1,309	£1,963	£2,618	£3,927	£5,236
Net medicine acquisition costs - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed					

The company estimates that net resource implications arising from the introduction of Sixmo® will lead to a saving of £10,482 in Year 1, increasing to a saving of £41,929 in Year 5. This is predominantly a consequence of a reduction in administration costs

and the number of addiction clinic visits. These resource type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company has also factored mortality into the calculations.
- It is uncertain how the estimates for uptake have been calculated.
- The company assumes a constant prevalence over the five years; it is uncertain how realistic this assumption is for the targeted population. The company suggests patients on ORT are continuously dropping on and off treatment, therefore discontinuation is already captured in the estimated annual treated patient numbers. However, this is likely an oversimplification, which has the potential to introduce uncertainty in budget impact estimates.
- Further sensitivity analyses would have been beneficial to include exploration of alternative market share assumptions.
- The indication for Sixmo® identifies this formulation as being suitable for stable patients who are also receiving medical, social and psychological support. If such support is routinely delivered during addiction clinic visits, it's questionable whether it is reasonable to assume a lower frequency of visits for patients receiving Sixmo®. The resource use savings predicted for Sixmo® resulting from a reduction in addiction visit clinics may therefore be an overestimate, and consequently may introduce bias into these estimates.
- The uncertainty related to resource use estimates identified in the cost-utility analysis is also a feature of the budget impact analysis.

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