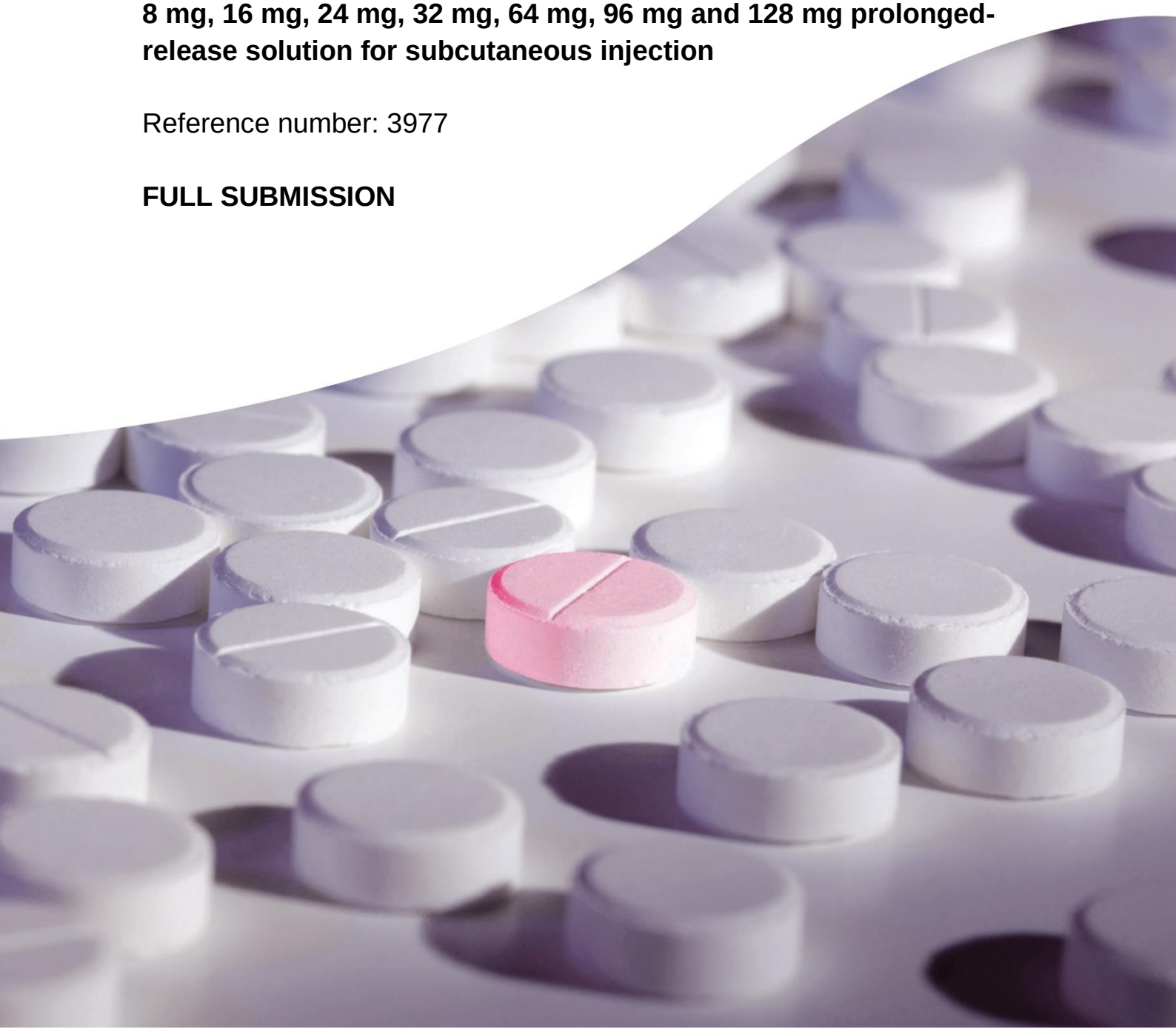
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Buprenorphine (Buvidal®)
8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg and 128 mg prolonged-release solution for subcutaneous injection

Reference number: 3977

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).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2182 6900

This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Buprenorphine (Buvidal®) 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg and 128 mg prolonged-release solution for subcutaneous injection. Reference number: 3977. June 2019.

AWMSG Secretariat Assessment Report
Buprenorphine (Buvidal®) 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg and 128 mg prolonged-release solution for subcutaneous injection

1.0 KEY FACTS

Assessment details	Buprenorphine (Buvidal®) for the 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. Buprenorphine (Buvidal®) is a prolonged-release subcutaneous injection administered weekly or monthly.
Current clinical practice	Treatment options for maintenance therapy are oral methadone, sublingual buprenorphine and sublingual buprenorphine/naloxone.
Clinical effectiveness	Buvidal® prolonged-release subcutaneous injection was non-inferior to sublingual buprenorphine/naloxone for the mean percentage of opioid-negative urine samples and the responder rate (defined as having no evidence of illicit opioid use at most assessments). The study was limited to a 24 week treatment time frame and long-term efficacy is unclear. Buvidal® offers advantages of being administered weekly or monthly. This reduced administration may be beneficial where there is risk of misuse, or there are concerns regarding compliance and retention rates. Some patients may prefer not having to attend for daily consumption. Buvidal® has to be administered by a health professional.
Cost-effectiveness	A cost–utility analysis compares Buvidal® with sublingual buprenorphine/naloxone in the treatment of opioid dependence within a framework of medical, social and psychological treatment. The company base case suggests that Buvidal® dominates sublingual buprenorphine/naloxone with a cost saving of £298 and an additional 0.034 quality-adjusted life-years gained. Buvidal® remained dominant in all scenario analyses with a 99.7% probability of being the most cost-effective option at a £20,000 willingness-to-pay threshold in probabilistic sensitivity analysis. The company has not provided deterministic sensitivity analyses for the cost–utility analysis. The cost difference between Buvidal® and sublingual buprenorphine/naloxone is driven by the reduction in fees associated with regular dispensing of subcutaneous Buvidal® (professional, establishment, controlled drug and supervised consumption). This was based on Welsh clinical expert opinion, due to a lack of published evidence and any deviation of these assumptions from routine practice will introduce bias of unknown proportions. Data are limited on frequency of routine dispensing and utilities.

Budget impact	The company base case suggests an additional cost of £71,391 in Year 1, increasing to £464,042 in Year 5. The base case also predicts NHS resource savings valued at £92,290 in Year 1, increasing to £599,884 in Year 5. The budget impact analysis does not take into account new incidence, mortality and treatment discontinuation. Sensitivity analysis showed that changes to market share and acquisition cost lead to budget impact estimates between £12,267 and £130,515 in Year 1 increasing to between £79,737 and £848,347 in Year 5.

This assessment report is based on evidence submitted by Camurus AB and an evidence search conducted by AWTTC on 8 to 9 April 2019.

2.0 BACKGROUND

2.1 Condition and clinical practice

Opiate dependence can cause a wide range of health and social problems for the individual and the wider community. In addition to the risks of accidental overdose, and the spread of blood-borne viruses such as HIV and hepatitis B and C due to the sharing of injecting equipment, there is also a clear association between illicit drug use and crime[1]. Pharmacological interventions used for opioid-dependent people are broadly categorised as maintenance (substitution), detoxification or abstinence. The aims of maintenance treatment are to provide stability and enhance overall function for the individual by reducing craving and preventing withdrawal, eliminating the hazards of injecting, and removing the preoccupation with obtaining illicit opioids. Opioid dependence is a long-term chronic condition with periods of remission and relapse that requires long-term treatment[2].

The UK guidelines on clinical management of drug misuse and dependence recommend oral methadone, sublingual buprenorphine and buprenorphine with naloxone in a combined sublingual tablet as options for maintenance therapy[3]. The formulation of buprenorphine with naloxone reduces the likelihood of the sublingual formulation being misused as the naloxone has minimal effect sublingually but is liable to precipitate withdrawal in an opiate-dependent patient if injected, therefore discouraging injection of the tablet formulation. The guidelines do not recommend one drug over the other. They advise that clinical factors such as adverse effects, previous experience, and patient preferences and consideration of the risk of diversion, overdose, practicalities of supervised consumption are taken into account on a case by case basis when choosing which medication to prescribe. Dose induction aims to reach a stable dose of opioid that avoids both intoxication and withdrawal[3]. Induction should be supported by supervised consumption which is relaxed only when appropriate to an individual's needs and risks[3].

2.2 Medicine

Buvidal® was granted marketing authorisation by the European Medicines Agency (EMA) in November 2018 for the treatment of opioid dependence in adults and adolescents aged 16 years or over within a framework of medical, social and psychological treatment. Buvidal® is formulated as a weekly or monthly prolonged-release subcutaneous injection[4].

Buprenorphine has both partial opioid agonist and opioid antagonist activity, binding to the mu and kappa opioid receptors of the brain[4]. Its efficacy in maintenance therapy is

attributed to its slowly reversible properties with the mu opioid receptors, producing a milder, less euphoric and less sedating effect than full opioid agonists such as methadone[1,4].

2.3 Comparators

The company suggests that subcutaneous Buvidal® would be positioned alongside sublingual buprenorphine/naloxone formulations due to its reduced potential for misuse, and could displace oral methadone or sublingual buprenorphine and be used as first line therapy or for patients switching their ongoing maintenance treatment[5,6].

The comparator included in the company submission was sublingual buprenorphine/naloxone. The company did not provide a comparison with oral methadone or sublingual buprenorphine.[7]

2.4 Guidance and related advice

- NICE evidence summary (2019): Opioid dependence: buprenorphine prolonged-release injection (Buvidal®)[8]
- Welsh Government substance misuse strategy for Wales (2008-2018): Working together to reduce harm[9]
- Department of Health UK guidelines on clinical management (2017): Drug misuse and dependence[3]
- NICE quality standard (2012): Drug use disorders in adults[2]
- NICE technology appraisal guidance (2007): Methadone and buprenorphine for the management of opioid dependence[1]

The All Wales Medicines Strategy Group (AWMSG) recommended with restrictions the use of buprenorphine/naloxone (Suboxone®) in 2008[7].

2.5 Prescribing and supply

The All Wales Therapeutics & Toxicology Centre (AWTTC) is of the opinion that, if recommended, buprenorphine (Buvidal®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 CLINICAL EFFECTIVENESS

The company's submission included results from the pivotal phase III study HS-11-421 which compared the efficacy of Buvidal® with sublingual buprenorphine/naloxone in untreated outpatients and results from a 48 week study (HS-14-499) evaluating the safety and tolerability efficacy of Buvidal®[6]. The other studies included in the company submission related to phase II studies, dose finding studies and an injection site study and will not be discussed further.[10]

3.1 HS-11-421

This was a randomised, double-blind, double-dummy, multi-centre, phase III clinical trial designed to evaluate the non-inferiority of weekly and monthly subcutaneous buprenorphine (Buvidal®) compared to daily sublingual buprenorphine/naloxone for the treatment of opioid dependence in treatment-seeking adults aged 18 to 65 years diagnosed with moderate-to-severe opioid dependence (n=428) as defined by the American Psychiatric Association diagnosis and statistical manual of mental disorders[11,12]. Patients were excluded if they received pharmacotherapy for opioid dependence within 60 days or any investigational drug within four weeks of the start of the trial[11].

Participants were randomised into one of the two treatment groups in a 1:1 ratio. One group received daily sublingual buprenorphine/naloxone plus scheduled placebo subcutaneous injections (n = 215) while the other group received scheduled subcutaneous injections of Buvidal® plus daily sublingual placebo (n = 213); injections were administered weekly in phase 1 (treatment weeks 1 to 11) and monthly in phase 2 (treatment weeks 12 to 24). Appropriate doses were established during an initiation week. All participants were given open label sublingual buprenorphine/naloxone equivalent to 4 mg buprenorphine before randomisation on day 1. After randomisation, participants received either subcutaneous Buvidal® injections of 16 mg (day 1) and 8 mg (day 4) plus daily sublingual placebo, or subcutaneous placebo injection (days 1 and 4) plus sublingual buprenorphine/naloxone 4mg (day 1) and sublingual buprenorphine/naloxone 16 mg (days 2 to 7). Individuals were allowed to return to the clinic for additional doses if withdrawal symptoms were still present. Individuals were required to make weekly scheduled clinic visits where subcutaneous injections were administered (placebo or Buvidal® 16 mg, 24 mg or 32 mg buprenorphine), a weekly supply of sublingual medicine was provided (placebo or sublingual buprenorphine/naloxone 8 mg, 16 mg or 24 mg buprenorphine equivalent) and additional dose adjustments made if appropriate. Efficacy and safety outcome measures were assessed at each weekly visit. On entering phase 2 at treatment week 12, individuals were transitioned to a monthly dose of subcutaneous Buvidal® based on the dose being received at the end of phase 1 and the daily dose of sublingual placebo was continued. Outcome measures were taken at monthly scheduled visits, when the subcutaneous injections were administered, and at three random visits. Individuals were transitioned to standard care sublingual buprenorphine/naloxone at the end of phase 2 (treatment week 24) and were followed up for a further four weeks[11].

The primary outcomes were the mean percentage of urine samples with test results negative for illicit opioids for treatment weeks 1 to 24 and the responder rate. A responder was defined as having no evidence of illicit opioid use (according to urine test results and a self-report of drug use) at treatment week 12 and for at least two of three assessments at treatment weeks 9 to 11, and for at least five of six assessments in treatment weeks 12 to 24, including month six. Opioid-negative urine samples favoured Buvidal® by a treatment difference of 6.7 (95% confidence interval (CI): –0.1 to 13.6; $p < 0.001$) and percentage of responders favoured Buvidal® by a treatment difference of 3.0 (95% CI: −4.0 to 9.9; $p < 0.001$)[11].

Secondary outcomes included the cumulative distribution function (CDF) of percentage urine samples negative for illicit opioids, the time to sustained abstinence from illicit opioid use and retention rate. CDF was calculated from an individual's 15 urine samples taken over the course of the study with missing samples imputed as positive. The overall median cumulative percentage of negative urine samples over time was 6.7% for sublingual buprenorphine/naloxone and 26.7% for Buvidal®, ($p=0.008$) demonstrating the superiority of Buvidal®)[5,6]. Retention rate (treatment difference −1.8, 95% CI: −11.2 to 7.6; $p=0.006$) was non-inferior [5,11].

3.2 Safety information

Study HS-11-421 did not highlight any specific safety concerns[5]. The long-term safety profile of Buvidal® was observed in one open-label multicentre study (HS-14-499) and was generally consistent with the known safety profile of sublingual buprenorphine/naloxone except for injection site reactions. These were generally mild to moderate in severity and rarely led to discontinuation of Buvidal® [6]. The majority of adverse events reported apart from injection site reactions were headache, nausea, urinary tract infections and constipation and rates were similar in both the Buvidal® and sublingual buprenorphine/naloxone groups. Other adverse events most frequently reported for buprenorphine include hyperhidrosis, insomnia and pain[4].

3.3 AWTTC critique

- Prolonged-release subcutaneous buprenorphine (Buvidal®) was shown to be non-inferior to sublingual buprenorphine/naloxone in the mean percentage of opioid-negative urine samples and the responder rate and was shown to be superior to sublingual buprenorphine/naloxone by CDF of percentage urine samples negative for illicit opioids.
- The company did not provide a comparison with oral methadone or sublingual buprenorphine and these may be displaced by Buvidal®. The company anticipate that Buvidal® will displace buprenorphine/naloxone formulations with reduced potential for abuse however clinical experts have advised it could displace all current treatment options.
- Buvidal® provides a treatment option which does not require supervised dispensing. This may be beneficial where there are difficulties organising supervised consumption or where there is concern about the risk of medicines being diverted. The company suggests that treatment with Buvidal® may reduce stigma associated with attending for daily supervision and may support adherence as individuals attend a healthcare setting for weekly or monthly injections rather than daily attendance for oral consumption. This may reduce inconvenience for individuals, enabling less disruption of employment, education and/or life. However, there would be less interaction with a health professional with weekly and monthly administration and some patients may value.the daily interaction with a health professional.
- Some people may prefer not to use an injectable opioid substitute and prefer oral therapy.
- Buvidal® has to be administered by an appropriate medical professional and appropriate staffing and facilities need to be available to administer it.
- Participants received expenses to attend study visits and there is uncertainty as to the impact this had on study retention rates.
- The EMA highlight that the key study was limited to a 24-week treatment time frame and considering over one fifth of individuals remain on maintenance therapies for five years or more, the long-term efficacy of Buvidal® is unclear.

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost–utility analysis (CUA) comparing prolonged-release subcutaneous buprenorphine (Buvidal®) (50 mg/ml weekly or 356 mg/ml monthly) with sublingual buprenorphine/naloxone (maximum of 24 mg buprenorphine daily), in adults and adolescents aged 16 years or over for the treatment of opioid dependence within a framework of medical, social and psychological treatment[6].

The CUA takes the form of a Markov model, comprising one week cycles. The model adopts a one year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are not discounted as the time horizon does not exceed one year. The model is characterised by five health states: on opioid dependence therapy not using illicit opioids, on opioid dependence therapy using illicit opioids, off opioid dependence therapy not using illicit opioids, off opioid dependence therapy using illicit opioids, and death. Patients enter the model in either the 'on opioid dependence therapy using' (either injected or not) or 'on opioid dependence therapy not using' states, and receive either prolonged-release subcutaneous buprenorphine or sublingual buprenorphine/naloxone at flexible doses. Patients can discontinue opioid dependence therapy at any point transitioning to the 'off opioid dependence therapy'

health states and transition to death from any health state.

The treatment retention and illicit drug use data used to inform the transition probabilities are derived from extrapolating data for the subgroup of patients using street drugs from the HS-11-421 study[11]. Observed data were fitted to a variety of common parametric distributions, and goodness-of-fit statistical tests were conducted. The Weibull function was selected for the base case and validated using the longer-term follow-up data from study HS-14-499 and published data[10,13,14].

Opioid dependence therapy patient-specific mortality was taken from literature and assumed to be identical in both model arms[15]. Injection site reactions were included as adverse events expressed as event rate per patient per year and considered self-managed. As such, while a disutility was applied, no costs were assumed. No other moderate to severe drug-related events were considered because they were similar in both pivotal trial arms and assumed identical in the model.

Treatment acquisition costs for Buvidal® were supplied by the company. The recommended starting dose of Buvidal® was 16 mg, with one or two additional 8 mg 'top up' doses at least one day apart, to a target dose of 24 mg or 32 mg during the first treatment week (initiation week). The recommended dose for the second treatment week was the total dose administered during the initiation week.

Treatment with monthly Buvidal® was started once patients were stabilised on weekly treatment (after four weeks or more). Comparator costs were calculated to be £0.36 per mg, based on the NHS drug tariff and dispensed prescription costs and volumes from November 2018 Welsh prescription cost analysis[16,17]. The average dose per day was obtained from the HS-11-421 trial 'street drug' subpopulation[11]. Buvidal® was assumed to be administered during routine visits to substance misuse clinics. As such, controlled drug fees, dispensing fees and supervised administration fees were not considered. Injections were costed as 10 minutes of a substance misuse nurse's time sourced from Personal Social Services Research Unit (PSSRU) unit costs[18]. Sublingual buprenorphine/naloxone administration costs include professional, establishment, controlled drug and supervised consumption fees which are costed using the NHS drug tariff and information from Community Pharmacy Wales[16,19]. Daily supervised dispensing and consumption was assumed throughout the time horizon for patients using illicit opioids and assumed to taper off after the first three months for non-users of illicit opioids based on clinical guidelines and expert opinion[20]. Healthcare resource use included the number of substance abuse clinics and urine tests based on expert opinion, GP and A&E visits and mental health related inpatient and outpatient visits[13], costed using PSSRU[18] and NHS reference costs[21]. Hospitalisation frequency was taken from the National Treatment Outcome Research Study (NTORS) study with length of stay obtained from Connock et al. 2007 and costs extrapolated from Scottish data[13,22,23].

No utility data were collected in the pivotal study[11]. Mean EQ-5D utilities for illicit drug users and non-users are therefore taken from published evidence[13]. Utility decrements of three day duration are applied for injection site reactions[24].

Probabilistic sensitivity analysis was conducted to test the influence of the uncertainty of individual parameters on the model results. Scenario analysis explored the cost-differences between Buvidal® and sublingual buprenorphine/naloxone under the assumption of equal efficacy (cost-minimisation analysis).

4.2 Results

The results of the base case are detailed in Table 1. When compared with sublingual buprenorphine/naloxone, Buvidal® is dominating as it is £298 less costly and produces an additional 0.034 quality-adjusted life-years (QALYs). The main cost differences can

be attributed to savings in pharmacy costs which offset the higher treatment acquisition cost. The incremental QALY gains are predominantly driven by the higher proportion of patients remaining off illicit drugs and the lower utility values assumed for illicit drug users.

Table 1. Results of the base case analysis

	Buvidal®	sublingual buprenorphine/naloxone	Difference
Medicine acquisition costs	£1,987	£1,578	£409
Administration costs	£111	£0	£111
Pharmacy costs	£0	£849	-£849
Healthcare costs (including hospitalisations)	£4,170	£4,139	£31
Total costs	**£6,268**	**£6,566**	**-£298**
Total QALYs	**0.714**	**0.680**	**0.034**
ICER (£/QALY gained)	**Buvidal® dominates**		
ICER: incremental cost-effectiveness ratio; QALY: quality–adjusted life–year			

Probabilistic sensitivity analyses indicate that Buvidal® has a 99.7% and 97.8% probability of being cost–effective at a threshold of £20,000 and £30,000 per QALY gained, respectively.

The company did not provide univariate sensitivity analysis. Results for the scenario analyses for the CUA are assessed in Table 2. This also includes the plausibility of the cost–minimisation analysis provided by the company.

Table 2. Results of scenario and sensitivity analyses

Scenarios	ICER	Plausibility
Retention based on Gompertz regression	**Buprenorphine dominates**	This scenario is plausible as the Gompertz function was found to have reasonable goodness-of-fit.
Retention based on exponential regression	**Buprenorphine dominates**	This scenario is plausible as the exponential function was found to have reasonable goodness-of-fit.
Time horizon extended to 5 years	**Buprenorphine dominates**	This scenario is plausible considering that 22% of patients remain on treatment for five years or longer. The base case time horizon of one year may therefore not capture all costs and benefits.
Time horizon extended to 5 years (using Gompertz regression)	**Buprenorphine dominates**	This scenario is plausible considering that 22% of patients remain on treatment for five years or longer and the Gompertz function was found to have reasonable goodness-of-fit.
Time horizon extended to 5 years (using exponential regression)	**Buprenorphine dominates**	This scenario is plausible considering that 22% of patients remain on treatment for five years or longer and the exponential function was found to have reasonable goodness-of-fit.
Inclusion of Hepatitis C infection costs and outcomes	**Buprenorphine dominates**	This is a plausible scenario as Hepatitis C infection is common in this patient group and will affect costs and outcomes.
Include trial HS-11-421[11] hospitalisation costs	**Buprenorphine dominates**	This scenario is plausible as the trial hospitalisation costs will reflect actual resource use in the patient group.

Scenarios	ICER	Plausibility
No daily supervision for illicit opioid users after 3 months	**Buprenorphine dominates**	The plausibility of this scenario depends on how it aligns with routine practice.
Week 24 retention value carried forward	**Buprenorphine dominates**	This scenario is less plausible as it is unlikely that 24-week results will be constant over time.
Week 24 % negative urines value carried forward	**Buprenorphine dominates**	This scenario is less plausible as it is unlikely that 24-week results will be constant over time.
Utilities obtained from HS-14-499[10]	**Buprenorphine dominates**	This scenario is implausible as no baseline values were collected in study HS-14-499 and the earliest data collection occurred in week 16 of the study which will bias results.
Equal outcomes assumed (Cost–minimisation analysis)	**Cost savings: £212**	This scenario lacks plausibility given that the pivotal trial found improvements in patients' illicit drug use. Furthermore, mode of administration and dosing differs between comparators. As such, the cost-minimisation analysis is inappropriate.

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model.

Limitations:

- The cost difference between Buvidal® and sublingual buprenorphine/naloxone is driven by the reduction in fees associated with regular dispensing of subcutaneous Buvidal® (professional, establishment, controlled drug and supervised consumption). The company state that this was based on Welsh clinical expert opinion, due to a lack of published evidence. Any deviation of these assumptions from routine practice will introduce bias of unknown proportions.
- No utility data was collected in the pivotal study and no baseline utilities were collected as part of study HS-14-499[10,11]. Utilities were therefore derived from literature without consideration of heterogeneity regarding study methods and population. This will introduce bias of unknown proportion.
- The economic evaluation extrapolates the 24-week follow-up data to one year based on proportional hazard survival models fitted to the retention and logistic regression of illicit drug use (urinalysis) data. While the company methods appear robust, valid and thorough, this data manipulation may introduce bias of unknown extent.
- The model assumes that patients who do not use illicit opioids while on treatment have a healthcare resource use equal to those retained on treatment as published by Connock et al. 2007[13]. These published values, however, did not distinguish between users and non-users. Furthermore, patients who use illicit opioids while on treatment are assumed to use the average of the healthcare resource of patients who were retained on treatment and those not retained on treatment[13]. It is unclear how accurately theses values will reflect the actual population in question.

- The company only provides deterministic sensitivity analysis for the cost-minimisation analysis. The impact of uncertainty in individual parameters in the CUA is therefore unknown.
- Extrapolation is inherently associated with uncertainty. While the choice of distribution was guided by statistical tests the company did not provide scenario analyses for the CUA to address the uncertainty associated with using the Weibull distribution by using other distributions that provided good statistical fit (exponential or Gompertz distribution).
- In the pivotal trial, patients experiencing a specific adverse event were counted only once, even though repeat events were possible. This may underestimate adverse event rate if repeat events would occur in the same patient. Furthermore, all adverse events other than injection site reaction were assumed identical between groups and excluded from the model. Any differences may therefore introduce bias[11]. Justification provided by the company was that while weekly injections were given in the trial until week 12, in routine practice, the switch to monthly injections could be made after week 4. They also state that exploratory analysis quadrupling adverse event rate did not change results.
- The pivotal trial included the monthly 160 mg dose of Buvidal® which will not be licensed in Europe. While use of this dose form comprised less than 1% of the monthly doses used in the trial and monthly doses are flat priced, the effect of the absence of this dose in practice on clinical outcomes is unknown[11].
- The model permits monthly doses of Buvidal® after four weeks, whereas in the pivotal trial, switching from weekly to monthly injections were only allowed after 12 weeks. The company notes that the monthly and weekly formulations can be regarded as interchangeable in terms of efficacy and the only impact to consider in terms of cost–effectiveness is the different frequency of administration costs, it is unclear how this discrepancy may impact discontinuation rate and cost–effectiveness.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost–effectiveness of Buvidal® versus sublingual buprenorphine/naloxone in the treatment of patients with opioid dependence who are suitable for buprenorphine formulation with reduced potential for misuse within a framework of medical, social and psychological treatment.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be 6,547 people receiving opioid dependence therapy in Year 1. This estimate is based on the number of patients receiving opioid dependence therapy in England and Wales in 2016[25] minus the number of patients receiving opioid dependence therapy in England in 2017–2018[26], and assumed to be constant over the five year time horizon. The company suggests that 33% of new opioid dependence therapy initiations were on buprenorphine-based treatment in Wales in 2017–2018[27], of which 15% are estimated to be on sublingual buprenorphine/naloxone [17]. It is expected that Buvidal® will have an uptake rate of 10% in Year 1, increasing to 65% in Year 5. This results in an assumed market share of 1.49% in Year 1, increasing to 9.65% in Year 5 applied to estimate the number of people likely to be prescribed Buvidal® 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. Basic sensitivity analysis was performed, altering the market share and medicine acquisition cost by ±20%.

5.2 Results

The budget impact is presented in Table 3. The company estimates that introducing Buvidal® would lead to an overall cost of £71,391 in Year 1, increasing to £464,042 in Year 5. This estimate incorporates cost differences resulting from the displacement of sublingual buprenorphine/naloxone. Sensitivity analysis showed that changes to market share and acquisition cost lead to budget impact estimates between £12,267 and £130,515 in Year 1 increasing to between £79,737 and £848,347 in Year 5.

Table 3. Company–reported costs associated with use of Buvidal® for the treatment of opioid dependency in adult patients.

	2019	2020	2021	2022	2023
Number of eligible patients (all licensed indications)	6,547	6,547	6,547	6,547	6,547
Uptake of new medicine (%)	1.49%	3.71%	5.94%	8.17%	9.65%
Number of patients receiving new medicine allowing for discontinuations	97	243	389	535	632
Medicine acquisition costs in a market without new medicine	£2,242,285	£2,242,285	£2,242,285	£2,242,285	£2,242,285
Medicine acquisition costs in a market with new medicine	£2,313,676	£2,420,763	£2,527,850	£2,634,936	£2,706,327
Net medicine acquisition costs	£71,391	£178,478	£285,564	£392,651	£464,042
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	**£71,391**	**£178,478**	**£285,564**	**£392,651**	**£464,042**

The company estimated that net resource implications arising from the introduction of Buvidal® will lead to a saving of £92,290 in Year 1, increasing to £599,884 in Year 5. This is a consequence of reduced pharmacy costs caused by the reduced need for daily dispensing and supervised consumption. 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. However, the company has not factored new incidence, population growth, treatment discontinuation and mortality into the calculations. The company have noted that 'new presentations' captured by drug treatment service statistics include not only patients who have *never* attended but also those who have already been through one or more courses of treatment in the past and potentially even in the same year, and thus may not reflect a true 'incidence'. Therefore, the company view is to assume that ODT patient prevalence (the net effect of new presentations, deaths and treatment dropouts) remains constant.
- In the absence of Welsh prevalence and incidence data regarding the number of people on opioid dependence therapy, the number of eligible patients was extrapolated from UK and English data 2016[25,26] and NHS Wales statistics[17,27]. It is uncertain how accurately this extrapolation reflects the situation in Wales.
- The budget impact considerations are limited to acquisition costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events).

REFERENCES

1. National Institute for Health and Care Excellence. Technology Appraisal 114. Methadone and buprenorphine for the management of opioid dependence. Jan 2007. Available at: https://www.nice.org.uk/guidance/ta114/resources/methadone-and-buprenorphine-for-the-management-of-opioid-dependence-pdf-82598072878789. Accessed Apr 2019.
2. National Institute for Health and Care Excellence. Quality Standard 23. Drug use disorders in adults. Nov 2012. Available at: https://www.nice.org.uk/guidance/qs23/resources/drug-use-disorders-in-adults-pdf-2098544097733. Accessed Apr 2019.
3. Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group. UK guidelines on clinical management. Drug misuse and dependence. Jul 2017. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/673978/clinical_guidelines_2017.pdf. Accessed Apr 2019.
4. Camurus AB. Buvidal®. Summary of Product Characteristics. Nov 2018. Available at: https://www.medicines.org.uk/emc/product/9705/smpc. Accessed Apr 2019.
5. European Medicines Agency. Assessment Report: Buvidal®. Procedure No.: EMEA/H/C004651. Dec 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/buvidal-epar-public-assessment-report_en.pdf. Accessed Apr 2019.
6. Camurus AB. Form B: Detailed appraisal submission. buprenorphine (Buvidal®). Mar 2019.
7. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1108. buprenorphine naloxone (Suboxone®) 8 mg/2 mg sublingual tablet, 2 mg/0.5 mg sublingual tablet. Jul 2008. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/70. Accessed Apr 2019.
8. National Institute for Health and Care Excellence. Evidence summary. ES19. Opioid dependence: buprenorphine prolonged-release injection (Buivdal). Feb 2019. Available at: https://www.nice.org.uk/advice/es19/resources/opioid-dependence-buprenorphine-prolongedrelease-injection-buvidal-pdf-1158123740101. Accessed Apr 2019.
9. Wales. Welsh Assembly Government. Working together to reduce harm: the substance misuse strategy for Wales 2008-2018. 2008. Available at: https://gweddill.gov.wales/topics/people-and-communities/communities/safety/substancemisuse/publications/strategy0818/?lang=en. Accessed Apr 2019.
10. Braeburn Pharmaceuticals. NCT02672111: Long-Term Safety Study of Buprenorphine (CAM2038) in Adult Outpatients With Opioid Use Disorder. Jun 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02672111. Accessed Apr 2019.
11. Lofwall MR, Walsh SL, Nunes EV 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 Internal Medicine.* 2018;178(6):764-773. Accessed Apr 2019.
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Accessed Apr 2019.
13. Connock M, Juarez-Garcia A, Jowett S et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technology Assessment.* 2007;11:1-171. Accessed Apr 2019.

14. Pinto H, Maskrey V, and Swift L. The SUMMIT Trial:. A field comparison of buprenorphine versus methadone maintenance treatment. *Journal of Substance Abuse Treatment.* 2010;39:340-352. Accessed Apr 2019.
15. Hickman M, Steer C, and Tilling K. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. *Addiction.* 2018;113:1461-1476. Accessed Apr 2019.
16. NHS Business Services Authority. NHS Electronic Drug Tariff 2019. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff Accessed Aug 2018.
17. NHS Wales. Prescription Cost Analysis. 2018. Available at: http://www.primarycareservices.wales.nhs.uk/prescription-cost-analysis. Accessed Feb 2019.
18. Curtis L, and Burns A. PSSRU Unit Costs of Health and Social Care. 2017. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/. Accessed Sep 2018.
19. Community Pharmacy Wales. Personal communication with company. 2019.
20. Department of Health. Drug misuse and dependence; UK guidelines on clinical management.
21. NHS Improvement. NHS reference costs 2017-2018. Available at: https://improvement.nhs.uk/resources/reference-costs/.
22. ISD Scotland. Drug Related Hospital Statistics. 2018. Available at: http://www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Drugs-Misuse/Drug-Related-Hospital-Statistics/. Accessed Dec 2018.
23. Godfrey C, Stewart D, and Gossop M. Economic analysis of costs and consequences of the treatment of drug misuse: 2-Year outcome data from the National Treatment Outcome Research Study (NTORS). . *Addiction.* 2004;99:697-707. Accessed May 2019.
24. Boye KS, Matza LS, and Walter KN. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *The European Journal of Health Economics.* 2011;12:219-230. Available at: INSERT DOI OF PAPER OR ACCESSIBLE REPRINT.
25. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). United Kingdom, Country Drug Report. 2018. Available at: http://www.emcdda.europa.eu/publications/country-drug-reports/2018/united-kingdom_en. Accessed Feb 2019.
26. Public Health England. Substance misuse treatment for adults: statistics 2017 to 2018 - GOV.UK 2018. Nov 2018. Available at: https://www.gov.uk/government/statistics/substance-misuse-treatment-for-adults-statistics-2017-to-2018. Accessed Nov 2018.
27. NHS Wales Informatics Service, Welsh Government, and Public Health Wales. Treatment Data - Substance Misuse in Wales 2017-18. 2018. Available at: https://gweddill.gov.wales/docs/dhss/publications/181108sub-misuse-wales1718nwisen.pdf. Accessed Apr 2019.