All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Buprenorphine/naloxone (Suboxone®) as substitution treatment for opioid dependence

Schering-Plough Ltd

Advice No: 1108

Recommendation of AWMSG

Buprenorphine/naloxone (Suboxone®) is recommended for restricted use within NHS Wales as substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. In accordance with NICE guidance such treatment should be considered in patients who are unsuitable for maintenance treatment with methadone.

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, lay perspective and discussions at the AWMSG meeting.

Date: Friday, 13th June 2008

The recommendation of AWMSG is:

Buprenorphine/naloxone (Suboxone®) is recommended for restricted use within NHS Wales as substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. In accordance with NICE guidance such treatment should be considered in patients who are unsuitable for maintenance treatment with methadone.

Key factors influencing the recommendation:

- The standard buprenorphine preparation is currently recommended by NICE as a cost effective option in eligible people who are unsuitable for maintenance treatment with methadone.
- AWMSG considers that Suboxone® should only be used in preference to buprenorphine where there are clear patient or service advantages.

Additional notes:
GPs have been increasingly encouraged to be involved in the treatment and care of opioid-dependent people. It is essential, however, that GPs should only prescribe within their expertise and should seek specialist advice when required. If necessary, GPs who are willing to prescribe can refer to the local drug dependency service for initiation of treatment, and then supervise maintenance therapy.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Suboxone® is indicated as substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction[1].

2.2 Dosing:
To avoid precipitating withdrawal, induction with Suboxone® or buprenorphine only tablets should be undertaken when objective and clear signs of withdrawal are evident (and a minimum of 24 hours after the last dose of methadone)[1].

Initiation therapy:
The recommended starting dose is one to two Suboxone® 2mg/0.5mg sublingual tablets. An additional one to two tablets of the Suboxone® 2mg/0.5mg may be administered on day one depending on the individual patient's requirement[1].

Dosage adjustment and maintenance:
The dose of Suboxone® should be increased progressively in steps of 2 to 8mg according to the clinical effect in the individual patient and should not exceed a maximum single daily dose of 24mg. After satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. Patients should be monitored following termination of treatment because of the potential for relapse.

Suboxone® sublingual tablets are placed under the tongue until dissolved, which usually requires 5 to 10 minutes. During the initiation of treatment, daily dispensing of buprenorphine is recommended. After a satisfactory stabilisation has been achieved the frequency of Suboxone® dosing may be decreased to dosing every other day at twice the individually titrated daily dose. In some patients, the frequency of dosing may be decreased to three times a week. However, the dose given on any one day should not exceed 24mg[1].

2.3 Market authorisation date: September 2006[2]

2.4 UK Launch date: December 2006

3.0 DECISION CONTEXT:

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 or C due to the sharing of injecting equipment, etc, there is also a clear association between illicit drug use and crime[3].

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. Detoxification refers to the process of safely eliminating the effects of opioid drugs from dependent opioid users in a way that minimises withdrawal symptoms[3,4]. Although abstinence may be one of the long-term goals of treatment, it is not always achieved, detoxification alone is rarely successful, especially at the first attempt[4,5].

Recent NICE guidance recommends methadone and buprenorphine (oral formulations), in flexible dosing regimens, as options for maintenance therapy in the management of opioid dependence. The decision about which drug to use should be made on a case by case basis and if both drugs are equally suitable, methadone should be prescribed as the first choice. The guidance further recommends that methadone and buprenorphine should be administered daily, under supervision, for at least the first 3 months, and supervision should be relaxed only when the patient's compliance is assured. Both drugs should be given as part of a programme of supportive care[3].

Suboxone® was not considered in the recent NICE guidance. It is a sublingual tablet that contains buprenorphine and naloxone in a 4:1 ratio[1]. Buprenorphine has both partial opioid agonist and antagonist activity, and provides a milder, less euphoric and less sedating effect than full opioid agonists such as methadone[3]. Naloxone is an opioid antagonist that displaces opioids from the opioid receptors. The rationale for the combined product is that, when taken sublingually as intended, the naloxone has very low bioavailability and does not diminish the therapeutic effect of the buprenorphine. However, if crushed and injected in an attempt to misuse the product, the naloxone has high bioavailability and is liable to precipitate withdrawal in an opiate-dependent patient, therefore discouraging further misuse[5].

As with the standard buprenorphine preparation, Suboxone® may potentially be administered less frequently than daily. A potential reduced need for supervised consumption, coupled with a reduced potential for diversion and misuse compared with methadone and buprenorphine, are important considerations. Suboxone® and the standard buprenorphine (Subutex®) 2mg and 8mg tablets, licensed for substitution in opioid drug dependence, are currently the same price[6].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The company submission describes an unpublished clinical trial of fixed-dose Suboxone® against fixed-dose methadone. This data is commercial in confidence. Other studies detailed in the submission were a placebo-controlled trial of fixed-dose Suboxone® and buprenorphine, and a clinical trial of flexible-dose buprenorphine (without naloxone) against methadone.

Collectively, the available evidence suggests that Suboxone® is as efficacious as the standard buprenorphine preparation, with no new safety concerns. It should be noted that the key efficacy trials presented in the company submission have been conducted outside of the UK, often in specialist settings and using close supervised consumption. Evidence of the use of Suboxone® under less stringent supervision is limited.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a cost-utility analysis of maintenance treatment based around a decision model. This compares Suboxone® against methadone, buprenorphine or no treatment over a 52-week period. There are several uncertainties in the assumptions made in relation to rates of retention in treatment, mortality rates with methadone treatment, and the assumed utility weights. In addition, the model assumes an optimistic reduction in the level of supervised consumption required with Suboxone® compared with methadone and buprenorphine. Collectively, these assumptions may favour Suboxone® and the reported sensitivity analyses do not adequately address these issues. The model was not provided and the model outputs have not been verified.

In the base-case analysis, the incremental cost per quality adjusted life year (QALY) gained with Suboxone® compared with methadone is reported to be £26,775. Suboxone® is reported to dominate buprenorphine as it is assumed to provide the same number of QALYs but is estimated to be less expensive. The no treatment arm would appear to be redundant in this analysis, as those people who are unable to be treated with methadone but who are suitable for Suboxone® would also be suitable for treatment with the standard licensed buprenorphine preparation.

Despite the many limitations of the evidence on cost-effectiveness provided in the company submission, Suboxone® is the same price as the standard licensed buprenorphine preparation (Subutex®) and is unlikely to be less cost effective than this. The standard buprenorphine preparation is recommended by NICE as a cost-effective option in eligible people who are unsuitable for maintenance treatment with methadone.

5.0 LIMITATIONS OF DECISION CONTEXT:

Clinical trials of substitute drugs often employ fixed drug doses that are lower than may be appropriate for retaining patients in long-term treatment. They are also usually conducted in specialist settings involving close supervised consumption supported by counselling and regular urinalysis. In addition, participants are often required to be free from serious organic and psychiatric illnesses. Given the context specific nature of drug use and the effectiveness of opioid treatments, there may be some limitations in the extent to which the results of clinical trials can be generalised to the population of opiate-dependent people in the UK.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY:

6.1 Clinical efficacy:

The company submission discusses an unpublished trial of Suboxone® against methadone, a trial of Suboxone® and the standard buprenorphine sublingual product against placebo, and a trial of the standard buprenorphine sublingual product against methadone.

6.1.1 Unpublished randomised controlled trial (RCT) of Suboxone® versus methadone maintenance treatment[7,8]

Data is academic and commercial in confidence.

6.1.2 RCT of Suboxone® and buprenorphine versus placebo[9,10]

This was a multi-centre, double-blind trial of fixed doses of Suboxone® 16mg/2mg and buprenorphine 16mg alone versus placebo. Participants (n=326) were randomised (1:1:1) to one of these treatments for 4 weeks, after which they could enter a 48–52-week open-label safety extension study. Induction and treatment during the 4-week double-blind phase was administered daily under supervision in a clinic setting on weekdays, with weekend doses provided as take-home medicines. All participants received up to one hour of counselling each week and were compensated ($10/day) for completing study assessments during the double-blind phase.

There were two primary endpoints in the double-blind phase of the study: the number of opiate-negative urine samples provided by participants relative to the expected number of samples (collected three times each week), and opiate craving score values measured using a 100mm visual analogue scale. Secondary endpoints included the subjects' and the clinicians' impressions of overall status since enrollment in the study and since the previous visit. Other secondary measures were the percentages of urine samples that were negative for other drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, and methadone), and participant retention.

The 4-week double-blind phase was closed early due to significant improvements with active treatment compared with placebo. For the 296 subjects who were not affected by the early closure of the study, retention in the study was high (243 subjects [82%] completed treatment) and was not significantly different between the active and placebo groups. The percentages of urine tests that were opiate-negative were 17.8% in the Suboxone® group and 20.7% in the buprenorphine group, as compared with 5.8% in the placebo group ($p<0.001$ for both comparisons against placebo). Both of the buprenorphine-based treatments also reduced the craving for opiates. During each of the four study weeks, the mean craving scores in the Suboxone® and buprenorphine groups were significantly lower than those in the placebo group ($p<0.001$ for both comparisons). This may be expected when comparing active treatment against placebo.

The overall health and well-being of the subjects in the combined-treatment and buprenorphine-only groups improved to a significantly greater extent than they did in the placebo group, as measured by the self-rated and the clinician-rated global-impression scales with which the participants' status was assessed each week ($p<0.001$ for both active groups versus placebo at all assessments). There was no significant difference between the active and placebo groups in the percentages of urine samples that were negative for other drugs of abuse.

Few efficacy data are available from the long term safety phase. A total of 472 subjects (including 268 who had participated in the 4-week double-blind trial) took part and received treatment with Suboxone®. Of these, 11 received treatment only in the 4-week double-blind phase, 385 received at least eight weeks of treatment and 261 received at least six months of treatment with Suboxone®. The percentage of opiate-negative urine samples ranged from 35.2% to 67.4% in multiple assessments. The overall rate of illicit opiate use was lower than that in the double-blind trial[9].

This study was not designed to compare Suboxone® against buprenorphine, but the EPAR considers that the results also indicate that Suboxone® is as effective as buprenorphine alone in the treatment of opiate dependency[10].

6.1.3 RCT of buprenorphine versus methadone[8,11]

This was a multi-centre, double-blind, double-dummy trial of flexible dose standard buprenorphine (no naloxone) against flexible dose methadone conducted in a clinic setting over a 13-week period. Of 405 randomised participants, 394 provide efficacy data. During the first six weeks, all doses were administered daily. From week 7 to 13, those participants randomised to buprenorphine received double doses on alternate days, with placebo provided on the intervening days; participants therefore still attended the clinic daily. Those who completed the 13-week study were eligible to enter open-label safety phases, taking the total treatment exposure to up to 104 weeks.

The primary efficacy measures were retention in treatment and abstinence measured by opioid-negative urine samples collected every two weeks. Overall, 54.8% of participants completed the 13-week double-blind trial. More methadone recipients were retained in treatment for the entire 13-weeks than were buprenorphine recipients (59% versus 50%), which the company submission states was statistically significantly different ($p<0.05$) and was due to a greater number of buprenorphine participants dropping out of the study in the first two weeks of treatment compared with methadone (20.3% versus 12.4%), possibly due to the slow titration up to an adequate dose[8]. The published paper states the overall retention rates were statistically significantly different only when assessed by a Cox proportional hazards model and this would not be statistically significant if adjusted for multiple testing[11]. There was no significant difference in retention rates in just the first 6 weeks of the study, or in just the period from week 7 to 13 when buprenorphine was administered on alternate days. There were no significant differences in the proportion of patients with opioid-negative urine samples at any point assessed.

Other efficacy measures included self-reported craving and heroin use. There were no significant differences between treatment groups for these measures. At week 6 the mean buprenorphine dose was 10.9mg/day increasing to 11.2mg/day during weeks 12 and 13. The mean dose of methadone in week 6 was 52.6mg/day, increasing slowly to 57.3mg/day in week 13. No data from the open-label extension phases are provided[8,11].

6.1.4 Points to note from these trials:

- The first two trials used fixed rather than flexible doses of Suboxone® and methadone. Current UK recommendations in relation to methadone and buprenorphine are to use flexible doses[3].

- Current UK clinical guidelines indicate that, after careful induction and dose stabilisation, there is a consistent finding of greater benefit from maintaining individuals on a daily dose between 60 and 120mg of methadone. There is less consensus about the effective dose levels of buprenorphine required to optimise outcome once dose induction and stabilisation have taken place but, in general, daily doses of between 12 and 16mg would seem appropriate for long-term prescribing[5]. In the first and third trials above, daily methadone doses (fixed at 45mg or 90mg in the first trial, and flexible dosing, with the mean dose used <60mg at all time points in the third), and the daily doses of buprenorphine (8 or 16mg in the first trial and mean <12mg at all time points in the third trial) were possibly suboptimal in some treatment arms. It is therefore unclear whether the differences in abstinence observed in the first trial between Suboxone® and methadone, or differences in retention rates during the third trial, would be achieved if the dose of each agent had been individually optimised in line with current guidelines.
- Participant recruitment in the first trial was halted before the intended 300 participants were enrolled due to sanctions imposed by the FDA on the associated University centre. There was an imbalance in the number of participants recruited to each treatment arm that, coupled with the fact that around three-quarters of participants dropped out before the end of the 17-week period, may have reduced the ability of the trial to detect differences in outcomes between groups.
- These trials were largely conducted in specialist treatment centres where treatment was extensively supervised on a daily basis.

6.2 Safety:

The RCT of Suboxone® and buprenorphine against placebo indicated that the overall rate of adverse events did not differ significantly between groups during the double-blind phase (78%, 85% and 80%, respectively)[9]. The most frequently reported adverse effects among the three groups were headache, withdrawal syndrome, pain, insomnia, nausea and sweating, of which only withdrawal syndrome was statistically significantly different between groups (25.2%, 18.4% and 37.4%, p=0.008, as may be expected in a trial versus placebo). Other adverse events that occurred at significantly different rates were diarrhoea (3.7%, 4.9% and 15.0%, p=0.005) and constipation (12.1%, 7.8% and 2.8%, p=0.03).

At total of 472 participants entered the long-term open-label phase of this study, of which 261 received Suboxone® for at least six months. 94.5% of the 472 participants experienced a treatment-emergent adverse event at some time while on treatment. The incidence of adverse events appeared to increase with dose received; however, there was also an increase in duration of exposure as the dose increased[10]. Eighty-one serious adverse events were reported. The most common (in 10 subjects) were increases in hepatic alanine or aspartate aminotransferase or lactate dehydrogenase levels that were judged to be not related (in 3 cases), possibly related (in 6 cases), or probably related (in 1 case) to the study medication. In 8 of these 10 cases, serologic evidence of hepatitis B or hepatitis C infection was present at base line. Non-serious adverse events reported by at least 20% of participants were headache, pain, withdrawal syndrome, infection, insomnia, back pain, and constipation. There were no clinically relevant electrocardiographic (ECG) changes, or haematological or chemical changes at any phase of the study[9].

The RCT of flexible dose buprenorphine (without naloxone) against methadone did not attempt to statistically compare adverse events but indicates that adverse event rates

were broadly similar for the two agents[11]. The NICE technology appraisal of methadone and buprenorphine found that pooled RCT data showed no significant difference in the rate of serious adverse events with methadone compared with buprenorphine maintenance treatment[3]. Indirect comparisons of data from cross sectional studies suggest that the level of mortality with buprenorphine may be lower than that with methadone maintenance treatment although other authors have commented that these data are unlikely to compare all related deaths[3].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Methadone and buprenorphine are the appropriate comparators for Suboxone®. The company submission considers that there are a significant number of patients in whom methadone would be inappropriate or intolerable and for whom the realistic alternative to Suboxone® is not to enter treatment at all[8]. However, in these circumstances, buprenorphine would seem to be the appropriate comparator for Suboxone®.

7.2 Comparative effectiveness issues:

Results of the only head-to-head trial of Suboxone® and methadone are as yet unpublished. This data is commercial in confidence.

The other supportive data provided in the company submission suggests that Suboxone® is as efficacious as buprenorphine in promoting abstinence and reducing craving[9,10]. The results of the RCT of buprenorphine against methadone[11] are broadly in line with the findings of the NICE review of RCTs of methadone and buprenorphine[3]. Pooled data indicated that overall retention in treatment was improved with flexible dose methadone compared with flexible dose buprenorphine (hazard ratio [HR] 1.40, 95% CI 1.15 to 1.69), but there was no significant difference in abstinence from illicit opioids as measured by urinalysis[3,11].

Most studies of methadone and buprenorphine to date have used fixed doses, rather than flexible doses recommended in current UK guidelines[3,5]. Often, the mean daily doses of methadone or buprenorphine used in the trials are lower than current UK clinical guidelines suggest are appropriate for maintaining individuals in treatment (e.g. the first and third trial described in the company submission). In addition, most trials have been conducted in specialist settings in other countries. Treatment practices may differ from those routinely used in the UK (e.g. use of financial incentives). However, despite the context specific nature of drug use and the effectiveness of opioid treatments, which have raised some concerns regarding the generalisability of trial results to the UK, the clinical experts consulted by NICE for the technology appraisal of methadone and buprenorphine considered that the outcomes of the trials could be generalised to opioid-dependent people in England and Wales[3]. In the absence of factors that would make methadone an inappropriate treatment for an individual, there appears to be little evidence to support using buprenorphine ahead of methadone in terms of its efficacy.

In terms of relative safety and adverse effects, it is generally agreed that there is less risk of opioid overdose associated with the use of buprenorphine than with oral methadone[5]. Indirect comparisons of data from cross sectional studies also suggest that the level of mortality with buprenorphine may be lower than that with methadone

maintenance treatment, although other authors have commented that these data are unlikely to compare all related deaths[3]. Methadone has a long and variable half-life that can lead to accumulation and delayed toxicity, often after several days of treatment. It is therefore essential that methadone induction starts with low doses and continues with slow titration; it may take several weeks to reach the desired dose[5]. Due to a risk of QT-interval prolongation, the Summary of Product Characteristics for methadone recommends ECG monitoring in those with risk factors and all those in who daily doses above 100mg are required[12].

In contrast to methadone, buprenorphine induction involves starting with a low dose, followed by rapid up-titration. However, as with methadone, there is a risk of toxicity if buprenorphine is used in combination with alcohol and/or other central nervous system suppressants (e.g. benzodiazepines)[1,5]. Clinical trials in the company submission have not observed reductions in the misuse of non-opioid drugs among participants.

The NICE technology appraisal of methadone and buprenorphine recommends daily administration under supervision for at least the first three months, and that supervision should be relaxed only when the patient's compliance is assured[3]. Daily installment prescribing and supervised consumption are useful for ensuring patients take their treatment as intended and reducing the diversion of prescribed drugs[5]. Buprenorphine and Suboxone® can be more difficult to supervise than methadone, as the sublingual tablets can take 5 to10 minutes to dissolve under the tongue[1,13].

The EPAR for Suboxone® states the product was developed as a take-home medication[10], and the Summary of Product Characteristics details its potential for alternate day dosing[1]. It should be noted that the key efficacy trials presented in the company submission have been conducted using close supervised consumption. A potential reduced need for supervised consumption, coupled with a reduced potential for diversion and misuse compared with methadone and buprenorphine are important considerations.

The Summary of Product Characteristics for Suboxone® also mentions detoxification with the product following stabilisation on maintenance treatment[1]. Clinical Knowledge Summaries suggests that, although methadone remains the gold standard for maintenance therapy, buprenorphine may be a preferred option in those who are likely to be in maintenance for a relatively short time, and are likely to proceed to detoxification soon[14].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by the use of buprenorphine/naloxone (Suboxone®) justify any associated increase in costs over relevant comparators.

8.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP identified a review of a cost-effectiveness analysis of high- or low-dose buprenorphine, buprenorphine/naloxone and methadone[15]. This analysis was based on treatment delivered in an Australian primary care setting in 1998 to 99 and used the number of heroin-free days over six months as the measure of effectiveness. Buprenorphine/naloxone was found to be more expensive but also more effective than methadone. The additional cost per heroin-free day was Australian $357 (95% CI: -1,520 to 2,367) for buprenorphine/naloxone. The review of this analysis identified a number of methodological weaknesses[16]. Given these weaknesses, the lack of consideration of the impact of treatment on quality of life, and the context specific nature of drug use and treatments, this cost-effectiveness analysis would seem to have limited applicability to the current decision problem.

Several cost-effectiveness analyses of buprenorphine (without naloxone) were identified in the company submission[8], but none are more recent or more comprehensive than the NICE technology appraisal of methadone and buprenorphine, issued in January 2007[3].

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission describes a cost-utility analysis of maintenance treatment based on a decision analytic model. This compares Suboxone® against methadone, buprenorphine or no treatment over a 52-week period. After entering treatment, individuals may remain on treatment, fall out of treatment or move to a state of death. Those who fall out of treatment are assumed to return to their pre-treatment opioid use and remain on this until the end of the 52-week period, or to move to a state of death. A cohort of 10,000 patients has been modelled[8].

Data from a non-comparative study of Suboxone® conducted in the USA in 1999 has been used to estimate retention rates for all active treatments in the model[17]. It is uncertain how adequately this would reflect the retention rates in treatment for the current Welsh population. The assumption that retention rates for Suboxone® would be the same for methadone recipients is also uncertain. These retention rates for methadone have been adjusted using Scottish methadone-related mortality rates reduced by 50%, which is also of uncertain applicability to the Welsh population. There are also issues with the assumed utility values, which were obtained from an Australian study of buprenorphine and methadone, in which the dose of methadone was lower than the optimal dose range currently suggested for maintaining patients in long term treatment. The doses of methadone, buprenorphine and Suboxone® assumed in the model are derived from different sources and it is unclear whether they would be directly equivalent. The drug acquisition costs assumed for Suboxone® and buprenorphine may be underestimated, and the assumed reduction in levels of supervised consumption required with Suboxone® are optimistic.

Therefore, there are several uncertainties and limitations in the assumptions used in the model, which collectively may favour Suboxone®. The reported sensitivity analyses do not adequately address some of these issues. The model was not provided and the model outputs have not been verified.

8.3.2 Population

The model considers opiate-dependent patients entering treatment and makes no assumptions about prior treatment history. The data used in the model is mainly derived from an unpublished, non-comparative safety study that was conducted in the USA in 1999 (commercial in confidence)[17]. This is supplemented by mortality data from Scottish statistics on drug use, and utility data obtained from a study of buprenorphine in Australia in 1999. Given the context specific nature of drug use and treatment, there may be some issues in generalising these data to the current population of opioid-dependent people in Wales.

8.3.3 Perspective and time horizon

In the base-case model, the perspective adopted is that of NHS Wales. Scenario analyses (called sensitivity analyses in the company submission) have explored the impact of including societal costs including criminal costs.

A one-year time horizon has been assumed in the model. Although maintenance treatment could potentially be long-term, the company submission considered it appropriate to consider a one-year time horizon as the health and cost differentials are short-term[8].

8.3.4 Comparator

The model compares four treatments: Suboxone®, methadone, buprenorphine (without naloxone) and no treatment. Methadone is acknowledged as the primary comparator in the analysis, but the company submission considers that there are a significant number of patients in whom methadone would be inappropriate or intolerable and for whom the realistic alternative to Suboxone® is not to enter treatment at all[8]. However, in these circumstances, buprenorphine would seem to be the appropriate comparator for Suboxone®. The no treatment arm would appear to be redundant for the current decision problem.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

Transition among the three states of the model (in treatment, fallen out of treatment and death) is based on the retention rates in treatment and the rates of drug- and methadone-related deaths obtained from several sources.

The model uses retention rates in treatment. Additional commercial in confidence data were made available to AWMSG[17]. The retention rates observed in this study with Suboxone® are assumed in the model to be the same for buprenorphine and methadone. There are several issues with this assumption. The retention rates seen in the health care setting of the study may not be generalisable to the usual setting in Wales. In addition, the assumption that retention rates would be the same for all active treatments is not supported by the majority of clinical trials that have assessed this outcome measure in individuals receiving buprenorphine and methadone. The pooled data reviewed for the NICE technology appraisal indicated that flexible dose methadone was significantly better at retaining patients in treatment than buprenorphine (HR 1.40, 95%CI 1.15 to 1.69)[3]. The selective use of data from the unpublished safety study of Suboxone® therefore introduces a degree of bias that may favour Suboxone®.

The retention rates for methadone have been adjusted in the model to take account of a potential increase in mortality while on treatment with methadone compared with buprenorphine or Suboxone®. In the model, it assumed that the mortality rate with methadone treatment would be 50% of that observed for overall methadone-related deaths in national statistics on drug use in Scotland. The methadone-related mortality data are referenced to the Scottish Drug Misuse Database but it is unclear how relevant this data is to the Welsh setting. In addition, it is not clear from the company submission the point in time to which the data relate, or how these data have been assumed to vary over the 52 weeks of treatment. The methadone-related mortality data that is provided in the company submission would suggest that the mortality rate is lowest in the first 4 weeks of treatment and increases substantially between week 44 and week 52[8]. However, this would seem to run counter to the considerable research evidence that suggests that the risks of methadone treatment are greatest during induction in the first two weeks of treatment and then fall to very low levels during maintenance treatment[5]. This is a further source of uncertainty, which has the potential to bias the model against methadone. Sensitivity analysis has explored the impact of removing the assumption of an increased risk of death with methadone.

For patients who have fallen out of treatment, mortality rates have been assumed to be the same across all treatment arms. Drug-related mortality rates have been assumed from a study of opiate users who entered treatment between 1990 and 1999 in eight European countries[18]. However, it is not clear how the assumed mortality rate used in the model has been derived from this source.

The retention rates as measured at specific time points in the unpublished open-label trial of Suboxone® have been assumed to change linearly between those time points. From this, daily transition probabilities have been derived. Presumably, the retention rates for methadone were adjusted with the above mortality data prior to conversion to daily transition probabilities.

8.3.5.2 Adverse events

Adverse events of treatment (other than methadone-related mortality) are not specifically mentioned in the description of the model[8]. The NICE technology appraisal of methadone and buprenorphine found that pooled RCT data showed no significant difference in the rate of serious adverse events with methadone compared with buprenorphine maintenance treatment[3]. On this basis, assuming no significant difference in adverse events between buprenorphine and Suboxone®, the lack of consideration of adverse events is unlikely to be major source of uncertainty in the model.

8.3.5.3 Utility weights

Utility values while on treatment have been derived from a 12-month, open-label trial of supervised buprenorphine against methadone conducted in Australia[19]. Utility scores were derived in this trial using time trade off techniques. For those receiving methadone, a utility value of 0.59 was obtained. For those receiving buprenorphine, a utility value of 0.62 was obtained, which in the current model is assumed to be the same for Suboxone® [8]. The utility values in this trial were not significantly different from baseline[19]. It is worth noting that the mean dose of methadone in this trial was lower than the 60 to120mg daily dose range that current UK guidelines suggest is appropriate for long term maintenance treatment. In contrast, the mean dose of buprenorphine used in the trial was within the 12 to16mg daily dose that would seem appropriate for long term maintenance[5,19].

Utility values while off treatment have been derived from the mean average of the utility values while on treatment (0.605), which has been adjusted using values adopted in a separate study of buprenorphine maintenance treatment in the USA[20]. In that study, utility values for patients who were in treatment were assumed to be 0.9 and utility values for injecting drug users not in treatment were assumed to be 0.8. These adjustments appear to have been quite arbitrary in that study[20]. The current model takes the ratio of these utility values (0.8/0.9) and uses this to adjust the mean average of the utility values while on treatment (0.605), yielding a utility value when not in treatment of 0.53778 for use in the current model[8]. These utility values are subject to considerable uncertainty. A sensitivity analysis explores the impact of varying the assumed utility values by +/-10%.

8.3.6 Healthcare resource utilisation and cost

In the base case analysis, costs and resource use are considered from the perspective of NHS Wales. Scenarios incorporating societal costs are explored in what the company describe as sensitivity analyses.

8.3.6.1 Drug costs

Additional commercial in confidence data regarding the dose of Suboxone® and buprenorphine was made available. The daily dose of methadone assumed in the model starts at 20mg on day 1 and increases in 10mg increments to 80mg at day 7; after which it remains at that level. This is not based on clinical trial data, but 80mg is within the suitable dose range for methadone maintenance treatment[5]. However, the dose of methadone should usually not be increased by more than 30mg per week[5].

The company submission states that unit costs per mg of drug have been applied using the British National Formulary (BNF) and company-collected data[8]. The cost per mg of methadone (£0.018) obtained from the BNF would seem appropriate as it is based on a 500ml bottle of non-proprietary methadone oral solution[6]. However, the cost per mg of Suboxone® and buprenorphine is based on the cost of 8mg tablets (expressed as buprenorphine, £0.36 per mg), which is lower than the cost per mg of the 2mg tablet (£0.48 per mg)[6]. At an assumed dose of 14.1mg, the use of the 8mg tablet cost per mg would underestimate the cost of Suboxone® and buprenorphine in the model.

8.3.6.2 Dispensing and supervision costs

The model considers the costs associated with dispensing and supervision of consumption. The assumptions made may be overoptimistic and favour Suboxone® compared with methadone and buprenorphine. The model assumes that all patients require full supervision in the first week of treatment and that around one-sixth of patients currently require supervision on two days or less per week, based on expert opinion (no further details provided). The model further assumes that 90% of patients on methadone or buprenorphine require some form of supervision, whereas only 40% of patients on Suboxone® will require some form of supervision[8]. Although Suboxone® may potentially reduce the need for supervised consumption, no justification is provided for the levels of reduction assumed in the model, which have the effect of favouring Suboxone® in the model.

Given that the model follows patients from initial induction treatment, it is unclear how closely the scenario modelled in the base case is aligned with current recommendations on supervised consumption. These imply that new patients should be required to take their daily doses under the direct supervision of a professional for a period of time (that may be around three months for methadone and buprenorphine), subject to assessment of patients' compliance and individual circumstances[5]. The model appears to assume that for Suboxone®, 60% of patients will only require one week of supervised consumption.

8.3.6.3 Adverse events

Adverse event data are not specifically incorporated in the model.

8.3.6.4 Other resources and costs in the base case analysis

The model assumes that all treated patients will attend six out-patient clinics, six counselling sessions and undergo urinalysis six times each year (referenced to company data, not verifiable) as part of their maintenance treatment. In addition, the costs of visits to A&E, community mental health services, GP visits, inpatient stay and mental health inpatient stay are considered for all patients in or out of treatment. It is not clear from where the annual rate of use of these items of healthcare resource have been obtained.

8.3.6.5 Other resources considered in "sensitivity analyses"

A range of societal costs have been considered in a sensitivity analysis. These include the criminal costs associated with burglary, drug possession/supply, fraud, robbery and shoplifting. The rates of these offences are reported to have been obtained from the National Treatment Outcomes Research Study[21]; however these are not verifiable from the cited reference. The rates of these offences are reported to have been multiplied by unit costs from a range of sources, but no further details are provided. The costs assumed in this analysis therefore cannot be verified.

The influence of the incorporation of other costs associated with hepatitis C and HIV is also explored. These costs have been incorporated by assuming that individuals who are not in treatment are at risk of contracting these viruses based on the current prevalence of the viruses in the population of injecting drug users. Those who are in treatment who provide opiate-positive urine samples are also assumed to be at risk of infection on the basis that they are injecting drugs. The probabilities of providing opiate-positive urine samples is reportedly derived from the unpublished RCT of Suboxone® versus methadone described in section 6.1.1. It is assumed that the buprenorphine probabilities are the same as those for Suboxone® [8]. A range of Welsh and UK data sources have been used to derive the prevalence and incidence of HIV and hepatitis C among injecting drug users, and the lifetime costs of treatment. The assumptions used in this analysis are subject to considerable uncertainty. For example, opiate-negative urine samples *per se* do not protect against the risks of contracting HIV and hepatitis C. Injecting drug users and those who remain in maintenance treatment may contract HIV and hepatitis C through other behaviours, and this is not considered in the analysis.

8.3.7 Discounting

No discounting has been applied due to the one-year time horizon (see 8.3.3).

8.3.8 Results[8]

8.3.8.1 Base case analysis: Suboxone® versus methadone

The incremental cost per quality adjusted life year (QALY) gained with Suboxone® is reported to be £26,775. This is based on incremental costs of £462 and a gain of 0.0172 QALYs.

8.3.8.2 Base case analysis: Suboxone® versus buprenorphine

Suboxone® is reported to dominate buprenorphine as it is assumed to provide the same number of QALYs but is estimated to be less expensive (by £284).

8.3.9 Sensitivity analysis[8]

8.3.9.1 One-way (univariate) sensitivity analyses

Several univariate analyses have been conducted to explore various assumptions and scenarios in the model.

8.3.9.1.1 Adjustment of the doses of Suboxone® and methadone

The stable dose of Suboxone® assumed in the model has been varied within the range 12mg to 24mg while keeping the base case dose of methadone (80mg) the same. The incremental cost per QALY for Suboxone® over methadone ranges from £17,922 to £68,508.

The stable dose of methadone assumed in the model has been varied within the range 60mg to 90mg while keeping the base case dose of Suboxone® (14.1mg) the same. The incremental cost per QALY for Suboxone® over methadone ranges from £30,898 to £24,728.

As outcomes are not linked to the drug doses in this analysis, this analysis simply varies the costs of Suboxone® and methadone relative to each other. Results are as would be expected and the analysis is of limited value.

8.3.9.1.2 Adjustment of the assumed utility values

The model is very sensitive to the assumed difference in utility values. In the base-case analysis, a utility value of 0.62 is assumed for Suboxone® (and buprenorphine) and 0.59 for methadone. When utility values are assumed equal at 0.62, the incremental cost per QALY for Suboxone® over methadone increases to £796,916. When the methadone utility value is increased by 10% and the Suboxone® value remains as in the base case, Suboxone® is dominated. The effect of adjusting the Suboxone® utility values by +/- 10% is as expected.

8.3.9.1.3 Suboxone® supervision levels

In the base-case analysis it is assumed that Suboxone® will only require supervision in 40% of cases. Varying the supervision levels up to 90% (as was assumed for methadone and buprenorphine) increases the incremental cost per QALY for Suboxone® over methadone to £39,032.

8.3.9.1.4 Other analyses

The influence of the assumptions of equal retention in treatment was explored by substituting the retention rates with those from the unpublished trial of Suboxone® versus methadone[7]. This had little influence on the model outputs. The NICE technology appraisal found consistent evidence that methadone improves retention rates compared with buprenorphine[3]. The extent to which retention rates have been adequately explored in the model is therefore uncertain.

Incorporation of societal costs, including criminal cost, has been explored. There are a number of uncertainties with the data used for this analysis but the modelled scenario slightly increased the incremental cost per QALY for Suboxone® over methadone to £29,384. Incorporation of the costs of hepatitis C and HIV has also been explored and is also subject to considerable uncertainty. The modelled scenario reduced the incremental cost per QALY to £23,912.

8.3.9.2 Multivariate and probabilistic sensitivity analysis

No multivariate or probabilistic sensitivity analyses have been conducted. This is a limitation of the evidence, as there are several assumptions in the model that are likely to interact to influence the model outputs.

8.4 Review of evidence on budget impact:[8]

8.4.1 Description and critique of the company's submission

The budget impact analysis is based on an assumed stable population of users in treatment. The analysis implicitly assumes that all those receiving maintenance treatment receive either methadone or Suboxone®; standard buprenorphine is not included in the model. This is a limitation of the analysis because, if Suboxone® was accepted for use in Wales, buprenorphine uptake would be expected to be affected. The analysis assumes the drug costs and rates of retention in treatment as used in the cost-utility model discussed in section 8.3, along with the assumptions on the levels of required supervised consumption. Therefore, due to several areas of uncertainty in the cost-utility analysis analysis, the results of the budget impact analysis must be interpreted with some caution. Moreover, the budget impact analysis that is presented does not actually indicate the net budgetary impact of the introduction of Suboxone®. It is simply a scenario costing exercise, which potentially underestimates costs.

8.4.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over the next five years[8].

8.4.3 Data sources

8.4.3.1 Prevalent and incident cases

The company submission states that there are no reliable estimates of the numbers of people who would be eligible for opioid maintenance therapy in Wales. Therefore, it is simply assumed that a population of 2,000 people would be eligible for opioid maintenance therapy, which includes new and existing clients. This population is assumed to remain stable over the next five years[8].

Details of people dependent on drugs, who may be eligible for opioid maintenance therapy, are available from alternative sources (Welsh National Database for Substance Misuse)[22]. A Health Needs Assessment published in 2006 by the National Public Health Service in Wales[23] provides a figure of 14.1 items per 1,000 Prescribing Units of methadone and buprenorphine prescribed by general practitioners in 2005/6.

8.4.3.2 Rates of adoption

The analysis assumes that all eligible patients undertake a course of opioid substitution therapy at the beginning of each year, with retention rates applied as in the cost-utility model in section 8.3. It is assumed that, initially, 5% of these 2,000 people will receive Suboxone®, and the remaining 95% receive methadone. The company submission states that buprenorphine is not considered due to the poor quality of data available to support forecasts about the likely future balance of treatments[8]. However, it should be noted that the data to support the whole analysis do not appear to be robust.

The analysis assumes that the average daily doses of Suboxone® and methadone would be 14.1mg and 80mg, respectively, as in the cost-utility model. Furthermore, it assumes that, following one week of daily supervised consumption, only 40% of Suboxone® recipients will require supervised consumption, compared with 90% of methadone recipients[8].

Two scenarios of Suboxone® uptake are considered: an increase of 1% and 2% each year in the proportion of people receiving Suboxone®. In the first scenario, 100 people would be eligible for Suboxone® in 2008, rising to 180 in 2012. In the second scenario, 100 people would be eligible for Suboxone® in 2008, rising to 260 in 2012[8].

8.4.3.3 Costs and resource use

The daily dose of Suboxone® is assumed to be 14.1mg (expressed as buprenorphine). The drug acquisition cost per mg of Suboxone® is based on the cost of the 8mg tablet (£0.36 per mg compared with the cost per mg based on the 2mg tablet which is £0.48[6]). The use of the 8mg tablet cost per mg to estimate the daily drug acquisition cost of Suboxone® in this analysis will lead to an underestimate.

The costs of supervised and unsupervised dispensing (pharmacy fees) are as estimated in the cost-utility model. The company submission highlights savings in the pharmacy fees with the use of Suboxone® instead of methadone.

8.4.4 Results

The estimate of the "budgetary impact" of the introduction of Suboxone® is based on costs taken from the cost-utility analysis discussed in section 8.3. These have been adjusted by the retention rates assumed in the cost-utility model. There are several uncertainties in the assumptions used in the cost-utility model (see section 8.3), which would mean that the results should be interpreted with caution. Moreover, the approach taken with the calculation of the budget impact appears to be a simple costing exercise for the scenario that is modelled. The "budget impact" reported in the company submission is simply the increase in costs each year over the assumed scenario of 5% uptake of Suboxone® in 2008, rather than being the net budgetary impact of the use of Suboxone® instead of the use of the comparator (methadone in this analysis).

Taking the scenario of a 1% increase in Suboxone® uptake, the way in which the company submission has presented the budget impact estimates implies that in 2008 there would be no budget impact and a small budget impact in subsequent years that would increase up to 2012 to £52,986 excluding pharmacy fees, or £14,612 including pharmacy fees.

These figures are incorrect and misleading. Using the assumptions of the company submission, if methadone was used in all 2,000 eligible people, the annual drug cost excluding pharmacy fees would be £524,620, and including pharmacy fees would be £2,234,700. In 2008, with an assumed 5% use of Suboxone® and 95% use of methadone, the annual drug costs excluding pharmacy fees would be £590,853, and including pharmacy fees would be £2,252,965. The net budgetary impact in 2008 would therefore be £66,233 excluding pharmacy fees, or £18,265 including pharmacy fees. In 2012, the net budgetary impact would be £119,219 excluding pharmacy fees, or £32,877 including pharmacy fees.

The budget impact for the scenario of 2% increase in uptake is similarly erroneous. The company submission implies no budgetary impact in 2008, and an impact of £105,973 excluding pharmacy fees, or £29,224 including pharmacy fees in 2012. Using the assumptions of the company submission, the net budget impact in 2008 would be £66,233 excluding pharmacy fees, or £18,265 including pharmacy fees. In 2012, the net budgetary impact would be £172,205 excluding pharmacy fees, or £47,489 including pharmacy fees.

All of these estimates are subject to considerable uncertainty and cannot be considered to be robust.

8.4.5 Sensitivity analysis

Sensitivity analysis has not been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

The Summary of Product Characteristics for Suboxone® states that treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction[1]. GPs have been increasingly encouraged to be involved in the treatment and care of opioid-dependent people. However, it is essential that GPs should only prescribe within their expertise and should seek specialist advice where needed. Most localities will have a clearly defined drug dependency service with a readily accessible entry point. Community drug teams implement treatment plans, monitor treatment, provide counselling, and promote needle exchange and other harm-reduction activities. If needed, GPs who are willing to prescribe can refer to the local drug dependency service for initiation of treatment, and then supervise maintenance therapy[14].

9.2 Related guidance:

Department of Health (England) and the devolved administrations. Drug Misuse and Dependence: UK Guidelines on Clinical Management. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive; September 2007 [the "*Orange book*"]. This highlighted that clinical experience with Suboxone was very limited at the time of writing[5].

9.3 Previous AWMSG/NICE advice:

National Institute for Health and Clinical Excellence. Methadone and buprenorphine for the management of opioid dependence. Technology Appraisal No. 114; January 2007[3].

National Institute for Health and Clinical Excellence. Naltrexone for the management of opioid dependence. Technology Appraisal No. 115; January 2007[24].

National Institute for Health and Clinical Excellence. Drug misuse: opioid detoxification. Clinical Guideline No. 52; July 2007[4].

National Institute for Health and Clinical Excellence. Drug misuse: psychosocial interventions. Clinical Guideline No. 51; July 2007[25].

9.4 Ongoing studies:

The company submission states that the trial of Suboxone®, submitted as Academic in confidence data, is expected to be submitted for publication in 2008. No other evidence is stated as being anticipated in the next 6 to 12 months[8].

9.5 Patient Interest Group information

A patient interest group submission by Drugaid was provided to AWMSG members.

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