

**buprenorphine/naloxone 2mg/0.5mg, 8/2mg sublingual tablet
(Suboxone^o)** **No.**
(355/07)

Schering Plough

9 February 2007

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

ADVICE: following a full submission

buprenorphine/naloxone (Suboxone^o) is accepted for restricted use within NHS Scotland for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

In the pivotal trial buprenorphine/naloxone was superior to placebo and had similar efficacy and safety to buprenorphine. There are currently no published trials comparing buprenorphine/naloxone with methadone.

Buprenorphine/naloxone is restricted to those patients in whom methadone is not suitable and for whom the use of buprenorphine is considered appropriate.

Overleaf is the detailed advice on this product.

**Vice-Chairman
Scottish Medicines Consortium**

Indication

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.

Dosing information

Initiation therapy: one to two tablets taken sublingually.

Dosage adjustment and maintenance: the dose should be increased in steps of 2-8mg (of buprenorphine) according to clinical effect of the individual patient and should not exceed a maximum single daily dose of 24mg (of buprenorphine).

Product availability date

December 2006

Summary of evidence on comparative efficacy

Buprenorphine is a partial opioid receptor agonist. The combination with naloxone, an opioid antagonist, is intended to discourage users from abusing buprenorphine by crushing and injecting the tablet, and is an established strategy for reducing the potential for intravenous misuse.

A four week double-blind, placebo-controlled efficacy trial has been conducted in the US in patients aged 18-59 years with a diagnostic criteria for opiate dependence according to Diagnostic and Statistical Manual of Mental Disorders 4th edition. Patients were randomly assigned to daily treatment with buprenorphine/naloxone 16/4mg, buprenorphine 16mg, or placebo sublingually for four weeks. Patients in the buprenorphine/naloxone group received buprenorphine 8mg and 16mg on days one and two to minimise the risk of naloxone-induced opiate withdrawal, and the combination thereafter. Patients in the buprenorphine group received 8mg on day one and 16mg thereafter. In addition to daily administration of medication at the clinic (weekdays) patients received counselling regarding HIV infection and up to one hour of individualised counselling per week. Weekend doses were dispensed on Fridays and were also provided for use on clinic holidays. The primary endpoints for the trial were the percentage of opiate-negative urine samples and subjects' self-reported craving for opiates (on a 100mm visual analogue scale, from "no craving" [0] to "most intense craving I ever had" [100]). Secondary endpoints included retention in treatment.

A total of 323 patients were enrolled and randomised to treatment. Due to early discontinuation of the trial, after statistically significant differences were shown between treatment and placebo groups, the full efficacy population was reduced to 296 patients (98, 101 and 97 treated with buprenorphine/naloxone, buprenorphine and placebo respectively). The percentage of urine samples that were opiate-negative was 17.8%, 20.7% and 5.8% in the buprenorphine/naloxone, buprenorphine and placebo groups respectively ($p < 0.001$ for both treatment groups vs. placebo). For each group the opiate craving scores were reduced to 30, 33 and 55 from baseline values of 62, 63 and 66 respectively ($p < 0.001$ for both treatment groups vs. placebo). The retention in treatment was 85%, 84% and 77% respectively.

An open label safety study with a treatment duration of 48-52 weeks, recruited 268 patients who had participated in the double-blind trial and 193 new patients. Patients were treated with doses of buprenorphine/naloxone up to 24/6mg daily. The percentage of opiate-negative urine samples ranged from 35% to 67% in multiple assessments. The overall rate of opiate use was lower than that in the double-blind trial, whereas the use of cocaine or benzodiazepines remained relatively constant.

The National Institute for Health and Clinical Excellence (NICE) released an assessment report; *Methadone and Buprenorphine for the Management of Opioid Dependence: A Systematic Review and Economic Evaluation* in 2006. Data were presented from seven randomised controlled trials (n=976) that directly compared flexible dosing of methadone with buprenorphine. The data indicate statistically significant superior retention in treatment with flexible dosing of methadone compared with flexible dosing of buprenorphine (Risk Ratio [RR] 1.20; 95% confidence interval [CI] 1.07, 1.33). There was no significant difference in the level of opiate abuse (based on morphine positive urines) between flexible dose methadone and buprenorphine (standardised mean difference = -0.12; 95% CI -0.26, 0.02). When comparable fixed doses of methadone and buprenorphine were considered it was found that methadone was more effective than buprenorphine with respect to retention in treatment, with the exception of low doses where the two drugs were comparable (RR 1.10; 95% CI 0.66, 1.54).

Summary of comparative safety

In the pivotal trial the overall rate of adverse events did not differ significantly between treatment groups (buprenorphine/naloxone 78%, buprenorphine 85%, and placebo 80%), with withdrawal syndrome, diarrhoea and constipation being the only events that were significantly different among the three groups. Fourteen serious adverse events were reported in 13 subjects (buprenorphine/naloxone 4; buprenorphine 3; placebo 7). Inpatient detoxification treatment was the most common (5 subjects), and suicidal ideation or a suicide attempt was reported by two subjects, both from the buprenorphine group. Changes in electrocardiograph, chemical and haematological tests were small and not clinically relevant. In the open label safety study the incidence of adverse events appeared to increase with dose; 68% (89/131) of patients taking buprenorphine/naloxone 4/1mg, 86% (339/394) of patients taking buprenorphine/naloxone 16/4mg and 96% (46/48) of patients taking buprenorphine/naloxone 24/6mg. However it was noted that an increase in duration of exposure occurred as the dose increased.

The scientific discussion of the European Public Assessment Report (EPAR) produced by the European Medicines Agency (EMA) concluded that the incidence of adverse events was comparable when buprenorphine was administered as monotherapy as compared to administration in combination with naloxone.

Summary of clinical effectiveness issues

There are no published trials comparing buprenorphine/naloxone with methadone. A randomised controlled trial comparing buprenorphine/naloxone with methadone is expected to be submitted for publication in the next few months.

The scientific discussion of the EPAR noted that successful detoxification can be obtained with buprenorphine/naloxone titrated downward to 2mg/day (of buprenorphine) before termination of therapy. However in some patients it may be necessary to titrate downward from 2mg, in small steps of 0.4mg before termination of therapy. The switch to 0.4mg of buprenorphine alone may be considered in this situation. Detoxification with a switch from buprenorphine/naloxone to buprenorphine alone will be monitored as part of the risk management plan submitted to the EMEA.

The lack of UK-based data has been highlighted as a limitation in the research evidence base and may limit how the results can be generalised for the UK.

The summary of product characteristics (SPC) for buprenorphine/naloxone includes advice on the use of less than daily dosing (every other day or three times a week) after satisfactory stabilisation has been achieved. In a trial comparing buprenorphine and methadone, when alternate day dosing of buprenorphine was included in the treatment plan, 85% of buprenorphine patients still in treatment at the time of the switch continued on alternate day dosing for the duration of the trial (a further seven weeks). A recent Cochrane review of methadone and buprenorphine, states that “given buprenorphine’s different pharmacological properties, it may have advantages in some settings and under some policies where its relative safety and alternate day administration are useful clinically compared with methadone”. The low abuse potential of buprenorphine/naloxone and a possible reduction in the need for supervised dosing are relevant factors to consider.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing buprenorphine/naloxone to three different alternatives: methadone, buprenorphine alone, and “no treatment”. A decision tree was used to model the costs and benefits over one year, including an NHS perspective and a societal perspective.

Clinical expert opinion in Scotland suggests methadone would be the most appropriate comparator. Clinical data were derived from an indirect comparison of randomised controlled trial (RCT) results. Compared to methadone, buprenorphine/naloxone cost an additional £600 but yielded an additional 0.02 QALYs, and on this basis the manufacturer estimated the cost per QALY gained to be £29,110.

There are several potential weaknesses in the method of calculating the result, however:

- (i) The indirect comparison of efficacy – while there is evidence buprenorphine/naloxone is equivalent to buprenorphine over 4 weeks, the equivalence of buprenorphine and methadone relies on a higher dose of buprenorphine. The NICE assessment report of buprenorphine versus methadone identified additional studies not considered in the manufacturer’s submission that led NICE to conclude that methadone was more efficacious.

- (ii) The use of utility values and adjustments to these from the literature was not transparent, though they generally anticipated that buprenorphine/naloxone resulted in quality of life improvements relative to methadone after six months treatment.
- (iii) Buprenorphine/naloxone dosing was based on the median dose within an open-label follow-up whereas methadone dosing was based on an RCT with buprenorphine – it was not clear that these doses produced equivalent efficacy. Mean dosing from the trial worsened the cost effectiveness of buprenorphine/naloxone.
- (iv) A sensitivity analysis of the same supervision rate between buprenorphine/naloxone and methadone worsened the cost effectiveness ratio relative to methadone to £40,000 per QALY, while applying Scottish prescribing and supervision costs and possible supervision rates tended to further worsen the cost effectiveness ratio.

The manufacturer's estimate of net cost per QALY is subject to considerable uncertainty. The sensitivity analysis submitted concentrated on different comparators, perspectives and supervision rates and fees. It did not adequately explore weaknesses in the basic clinical data. Additional head to head data from the trial of buprenorphine/naloxone against methadone would have done much to strengthen the manufacturer's case.

However buprenorphine for the management of opiate dependence has been in second-line use for many years. The addition of naloxone may give additional efficacy and safety benefits and comes at no additional cost compared to the use of buprenorphine alone.

Summary of patient and public involvement

Patient Interest Group Submission: Sign Post Forth Valley

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) released a technology appraisal: *Methadone and buprenorphine for the management of opioid dependence* in January 2007. In relation to maintenance therapy, it concluded that rates of retention on treatment with flexible dosing of methadone are superior to those with flexible dosing of buprenorphine, although there is no significant difference in illicit opioid use. The decision about which drug to use should be made on a case by case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person. If both drugs are equally suitable, methadone should be prescribed as the first line choice. This guidance does not relate to the buprenorphine/naloxone preparation.

Additional information: comparators

Methadone is indicated for the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant) and buprenorphine for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

Additional information: costs

Product	Usual daily maintenance dose	Cost per year (£)
buprenorphine/naloxone	12/3mg-24/6mg	1572-3145[†]
buprenorphine	12-24mg*	1747-3145
methadone (Physeptone 1mg/ml) oral	60-120mg*	294-589
methadone 10mg/ml injection	40-60mg**	700-1400

* Usual daily maintenance dose taken from *methadone and buprenorphine for the management of opioid dependence final appraisal determination* (NICE)

** Usual daily maintenance dose taken from SPC.

† Cost taken from company submission

Doses are shown for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer projected the budget impact of buprenorphine/naloxone on the basis of 1000 patients switching to this treatment in year 1 (i.e. 5% of the current 20,000 methadone patients), with a 1-2% annual increase in market share rising to between 1,800 patients and 2,600 patients by year 5. The gross drug cost was estimated at £925k in year 1, rising to between £1.7M and £2.4M by year 5. The net budget impact was estimated at £828K in year 1, rising to between £1.5M and £2.2M by year 5. Savings on pharmacy supervision fees may also be possible. The budget impact forecast does not take into account additional patients for whom methadone is not appropriate who may be treated with buprenorphine/naloxone.

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 12 January 2007.

Costs in the 'Cost of relevant comparators' section are based on prices available at the time the papers were issued to SMC for consideration. Further details are available on the SMC web site at <http://www.scottishmedicines.org.uk/updocs/Costing%20FAQs.pdf>

The undernoted references were supplied with the submission.

*Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D; Buprenorphine/Naloxone Collaborative Study Group. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med.* 2003 Sep 4;349(10):949-58*

National Institute for Health and Clinical Excellence, 2006. Methadone and Buprenorphine for the Management of Opioid Dependence: A Systematic Review and Economic Evaluation. Technology Assessment Report Accessed on 4/12/06. <http://www.nice.org.uk/page.aspx?o=335475>