Re-submission

buprenorphine transdermal patches 5, 10 and 20 microgram/hour 7-day formulation (BuTrans®) No. (234/06)

Napp Pharmaceuticals Ltd

05 December 2008

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 third re-submission

buprenorphine transdermal patches (Butrans®) are not recommended for use within NHS Scotland for the treatment of severe opioid responsive pain conditions, which are not adequately responding to non-opioid analgesics.

In the patient population considered in this submission, severe osteoarthritis pain in elderly patients whose pain is not adequately controlled by non-opioid analgesics, or for whom other analgesics are not suitable, buprenorphine transdermal 7-day patch was superior to placebo and similar in efficacy to World Health Organisation (WHO) 'Step 2' analgesic comparator agents.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of severe opioid responsive pain conditions which are not adequately responding to non-opioid analgesics.

Dosing information

One 5, 10 or 20 microgram per hour patch should be applied every seventh day. The lowest 5 microgram per hour patch should be used initially, although consideration should be given to the patient's previous opioid history. It is recommended that no more than two patches be applied at the same time, regardless of the patch strength. A new patch should not be applied to the same skin site for the subsequent 3 to 4 weeks.

Product availability date

30th September 2005

Summary of evidence on comparative efficacy

Chronic pain is defined as, pain of at least three to six months duration and which has persisted beyond the point at which healing would be expected to be complete or that occurs in disease processes in which healing does not take place. It may be continuous or intermittent. Buprenorphine is an opioid with mixed agonist-antagonist properties; it has partial agonist activity at the mu opioid receptor and antagonistic activity at the kappa opioid receptor.

Initially, the indication under consideration in this third resubmission is for severe osteoarthritis (OA) pain in elderly patients, whose pain is not adequately controlled by non-opioid analgesics, or for whom other analgesics are not suitable. The evidence considered is from three clinical trial reports specifically in OA pain plus two in chronic back pain and one in non-malignant pain all of which included patients whose pain was caused by OA. All studies used 5, 10 and 20 microgram per hour buprenorphine patches with titration to pain control.

Should the cost effectiveness of buprenorphine 7-day patches be established in the above indication, the manufacturer has suggested that the full marketing authorisation might be considered. They assert that if buprenorphine patches are non-inferior to a mild opioid such as codeine at Step 2 of the World Health Organisation (WHO) analgesic ladder, in an osteoarthritis 'model' of nociceptive pain then it would follow that they would be an effective Step 2 treatment for other pain models. The place in therapy suggested by the manufacturer is that buprenorphine patches could be used if other Step 2 analgesics fail or are unsuitable before moving up to more potent (Step 3) opioid doses. A further open-label study has been included to provide data on the maintenance of efficacy and discontinuation rates over time.

Osteoarthritis

Two of the studies in osteoarthritis pain were double-blind, randomised studies with an initial titration to pain control over 21 days followed by an assessment phase. The study in 315 patients with osteoarthritis of the knee or hip compared buprenorphine patches with placebo over a seven-day assessment phase. Significantly more patients in the buprenorphine group achieved the primary outcome of successful pain management, with failure defined as early discontinuation from the study due to ineffective treatment or a final score of poor or fair on a patient satisfaction with study medication scale (44% vs. 32%, p=0.036; adjusted odds ratio 1.66 (95% confidence intervals [CI], 1.04 to 2.69)). The active comparator study in 238 patients, with at least a one month history of OA of the hip and/or knee, compared buprenorphine patches with buprenorphine sublingual tablets (200 microgram six or eight

hourly to 400 microgram eight hourly). Paracetamol was permitted for breakthrough pain. Patients who achieved pain control during the 21-day titration phase entered the 28-day assessment phase. There was no difference between treatments for the primary outcome measure of the patients' current level of pain intensity as measured by the Box Scale (BS)-11 pain score (scale of 0-10 where 0 = no pain and 10 = pain as bad as you can imagine) in the morning, midday and evening on days 3 and 7 of the assessment period for the per protocol (PP) population (n=102). The CI for the mean difference between treatments were within the specified limits for equivalence (that is, ±1.5 boxes on the BS-11 scale). Patient age was considered as a covariate in the analysis. Of the 120 patients randomised to buprenorphine patches, 49 (41%) were aged 65 years or over. The mean pain scores for this subgroup of patients showed effective pain control and were not significantly different from those for patients under the age of 65. There was no difference between treatment groups in the secondary outcome measures including other measures of pain intensity, use of escape medication, sleep disturbance, quality of sleep and patient satisfaction with their medication.

A phase IV, open-label, randomised study in 220 elderly patients (≥ 60 years) with severe OA (primary site of the hip and/or knee) compared paracetamol (1g four times daily) plus buprenorphine patches (5 to 25 microgram/hour) with paracetamol plus codeine (co-codamol; two 8/500mg tablets four times daily to two 30/500mg tablets four times daily). At inclusion, patients had to have a score of ≥ 5 on the BS-11 scale and to be taking at least 1g of paracetamol per day or their maximum tolerated dose of paracetamol. Titration to optimum pain control was over a period of up to 10 weeks. Patients achieving optimal pain control entered a 12-week assessment period. Breakthrough treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. The primary outcome in the PP population (n=117) was the average daily pain intensity on the BS-11 pain scale, assessed each evening by the patient and summarised by age (60 to 64 years and ≥ 65 years). A number of secondary outcomes were assessed including use of escape medication. Mean BS-11 pain scores decreased by at least 3 boxes (from a mean of 7) in each treatment group by the end of the titration period. This improvement was maintained throughout the assessment period and was not significantly different between treatments, demonstrating non-inferiority. Patients in the buprenorphine plus paracetamol group required significantly less escape medication than patients in the co-codamol group. The results in the intention to treat (ITT) population supported those in the PP population.

Chronic back pain

The studies were of randomised, double-blind, active comparator design in patients with chronic back pain of > 2 months duration, that was not manageable with non-opioid analgesics alone. A stable dose of a non steroidal anti-inflammatory drug (NSAID) was permitted. In one study, buprenorphine patches (n= 46) were compared with an oxycodone 5mg /paracetamol 325mg combination, one to three tablets six hourly (n=43) or placebo (n=45). Around 39% of patients had pain due to OA and 21% were over 65 years old. Once an effective dose was established during a 21-day titration phase patients entered a 63-day maintenance phase during which they were assessed for 'pain on average' and 'pain right now'. The primary outcome, least squares mean change from baseline in the intention to treat (ITT) population, for both these measures, was significantly greater in the buprenorphine group than placebo for the maintenance phase. There was no significant difference between buprenorphine and oxycodone/paracetamol in primary outcomes or in the secondary outcome measure of discontinuation due to lack of efficacy.

In the second chronic back pain study, which compared buprenorphine patches with hydrocodone 2.5mg/paracetamol 250mg (one to three tablets six hourly), 270 patients were titrated to one of the three dose levels to provide acceptable pain control then continued on that dose for a 35-day assessment period. Pain due to OA was reported by 30% of these patients and 20% of patients were over 65 years old. The primary efficacy measures were the mean average pain intensity and patient satisfaction with medication for pain scores (patient global efficacy rating). The mean average pain intensities were similar in the respective groups, 5.96 and 6.04 (on a scale of 0 to 10); difference 0.08 (95% CI -0.60 to 0.44) and the difference between groups in the patients satisfaction with pain was 0.16 (95% CI -0.08 to 0.39) rated on a 0 to 4 scale, demonstrating equivalence and non inferiority.

Chronic non malignant pain

There was one randomised, double-blind, placebo-controlled study in patients with at least two months history of stable non malignant pain controlled by oral opioid combination analgesia. Patients discontinued their opioid therapy during a 3-day screening phase and were treated with paracetamol. The 267 patients were titrated to pain control using buprenorphine patches, before randomisation to buprenorphine or placebo for a 14-day assessment period. Stable NSAID therapy and paracetamol for rescue were permitted. Pain due to osteoarthritis was reported by 53% of patients. The primary outcome of the percentage of patients with ineffective treatment in the ITT population during the assessment phase was significantly greater in the placebo group, 65% (89/137) vs 51% (66/129) and the odds of having ineffective treatment were 1.79 (95% CI, 1.09 to 2.95) times greater in patients receiving placebo than in patients treated with buprenorphine (p=0.022).

An open-label study of up to 21 months, enrolled 385 patients who had previously been recruited to buprenorphine patch trials and had moderate pain at baseline. The primary objective was to assess safety and tolerability and to acquire clinically useful information. As patients had already been stabilised on their previous analgesic therapy, little change was expected, however small improvements from baseline in mean pain scores were observed throughout the study. Most patients started treatment with the 5 microgram/hour patch and just under half of patients (48%) required titration to the 20 microgram/ hour patch.

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

Summary of evidence on comparative safety

No new safety concerns were raised during the studies with buprenorphine patches 5, 10 and 20 micrograms/hour. Most adverse events were mild to moderate in intensity.

In the study with buprenorphine patches and sublingual tablets in patients with OA significantly fewer patients in the buprenorphine patch group reported an adverse event during treatment compared with those using the tablets (81% vs. 92%). The most commonly reported adverse events were nausea, dizziness, vomiting, somnolence, headache, constipation and asthenia. In the placebo-controlled studies, the incidence of application site reactions was the same in the placebo and the active patch groups suggesting that the reaction was likely to be due to the transdermal system itself rather than the buprenorphine component.

In the open label comparison with co-codamol a similar number of patients withdrew from the study (45% vs. 47%); more patients withdrew due to adverse events in the buprenorphine plus paracetamol group.

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

Summary of clinical effectiveness issues

There is a high prevalence of OA in the 65 years and over age group and treatment of elderly patients with chronic pain is an ongoing issue. Problems that arise due to co-morbidities and treatments and compliance with multi-drug regimens mean that continuous non-oral pain relief over a 7-day period may offer advantages in therapy.

Although licensed for severe pain, there is little comparative data against WHO Step 3 analgesics and the company suggest that buprenorphine 7-day patches may be used at Step 2 of the WHO analgesic ladder and this is in line with the comparators used in the clinical studies. In the four active comparator studies two of the comparators are not licensed in the UK, although similar equivalents are available, and sublingual buprenorphine tablets cannot be considered standard treatment for chronic pain. However, codeine does seem to be an appropriate comparator. The robustness of the evidence base is limited and assessment difficult due to the variation in trial design, significant discontinuation rates and the relatively short duration of the studies, despite this treatment being for a chronic condition. The one open label extension study did suggest that buprenorphine remained effective over time but a significant number of patients discontinued with only a smaller cohort of patients continuing 21 months of treatment.

The robustness of the evidence base is further tested by the restriction of the marketing authorisation in this resubmission to OA pain in elderly patients. To support the use in this population two active-comparator studies in osteoarthritis pain were submitted, one of which was a post-licensing open-label study, undertaken mainly in primary care centres in the UK. The primary outcome in both osteoarthritis studies showed a greater than 2-box reduction in the BS-11 score which is considered clinically relevant and in the open-label study significantly fewer patients required titration to the highest dose level in the buprenorphine patch arm compared to the co-codamol arm (6.6% vs. 29%). These studies also demonstrated that pain control in the 65 years and over group was as effective as in patients under 65 years. In addition, two studies in chronic back pain and one in non-malignant pain, included patients with osteoarthritis pain (ranging from 30-53% of patients included in these studies) and patients 65 years and over. Unfortunately, there is no information in these studies on outcomes for those patients who had osteoarthritis pain and were over 65 years.

A 7 to 10 day course of anti-emetic is advised when initiating treatment with buprenorphine patches, adding to the pill burden. However in patients who may be unresponsive or intolerant to codeine, or in patients in whom NSAIDs are not recommended, buprenorphine 7-day patch may offer an alternative. Once initiated, there is the potential for inappropriate continued use of this product without proper assessment. It is therefore important that regular assessment of clinical benefit and adverse effects are actively undertaken.

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

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of buprenorphine transdermal patches for use among osteoarthritic patients within the 'Step 3' of the WHO analgesic ladder. Patients in the analysis were assumed to have severe osteoarthritis, be over 65 and in need of a change in treatment from Step 2 (weak opioid plus non-opioid) to Step 3 (strong opioid plus non-opioid) of the WHO analgesic ladder. The analysis adopted relatively simple pairwise comparisons with fentanyl patches, oxycodone modified release, morphine modified release and placebo. This was assessed over a one year time horizon, with non-responders coming

off treatment after eight weeks. Responders continued with treatment experiencing a quality of life gain.

The base case clinical effectiveness estimate for buprenorphine transdermal patches was taken from the open-label trial among elderly patients with osteoarthritis to yield a responder rate of 55% (the proportion of patients continuing with treatment). Clinical effectiveness estimates for the strong opioids were derived from an informal literature review with a common responder rate of 60% being assumed. The clinical effectiveness estimate for placebo was drawn from a meta-analysis of placebo controlled trials of weak opioids, to yield a responder rate of 43%.

Quality of life data for responders was taken from the open-label buprenorphine transdermal patches trial. Drug dosing was drawn from that reported within the buprenorphine transdermal patches trial, and for the strong opioids from within the literature.

Morphine was estimated to be more effective but also more expensive than placebo, with an ICER of £4,375 per QALY. Buprenorphine transdermal patches were estimated to be more expensive and less effective than morphine, so were dominated. The other strong opioids were also dominated by morphine.

Excluding morphine as a comparator, buprenorphine transdermal patches were estimated to be more effective but also more expensive than placebo, with an ICER of £11,267 per QALY. Oxycodone was estimated to be more effective but also more expensive than buprenorphine transdermal patches, with an ICER of £17,180 per QALY. Fentanyl patches were significantly more expensive and unlikely to be cost effective. As a consequence, the manufacturer appeared to estimate morphine to dominate buprenorphine transdermal patches and oxycodone to be of reasonable cost effectiveness relative to buprenorphine transdermal patches within Step 3 of the WHO analgesic ladder.

An additional weakness of the analysis was considering buprenorphine transdermal patches within the Step 3 of the WHO analgesic ladder and related to this the clinical effectiveness data for buprenorphine transdermal patches being drawn from an open-label trial more relevant to the Step 2 of the WHO analgesic ladder. It might also have been possible to consider both the responder status and the degree of pain control, though the limitations of the informal indirect comparison might have made this difficult. Treatment sequences that considered the subsequent treatment of non-responders might also have been considered. The direct drug cost of fentanyl patches might have been overestimated if multiple simultaneous use of 25 microgram per hour patches within a trial would be replaced by higher dose patches in practice. Sensitivity analyses were inadequate, only considering the comparison with placebo.

Given this, the cost effectiveness of buprenorphine transdermal patches (7 day) has not been demonstrated for the position presented within the economics section of the submission.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In February 2008, the National Institute for Health and Clinical Excellence published Clinical Guideline no. 59 Osteoarthritis. This provides guidance on the care and management of adults with osteoarthritis. It states that: the evidence supporting the use of opioid analgesia in osteoarthritis is poor, and it must be noted there are virtually no good studies using these agents in peripheral joint osteoarthritis patients. There is little evidence to suggest that dose escalation of these agents is effective. There are also few data comparing different opioid formulations or routes of administration. Toxicity remains a concern with opioid use, especially in the elderly. However, it also states: If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in elderly people.

In 2008, Osteoarthritis Research Society International published its recommendations for the management of hip and knee osteoarthritis. Its main general recommendation is that the "optimal management of osteoarthritis requires a combination of non-pharmacological and pharmacological modalities". Twenty-five recommendations were issued. Guide number 20 proposes that "weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients, where other pharmacological agents have been ineffective, or are contra-indicated". Also "benefits associated with the use of opioids were limited by the frequency of side effects. Overall in the reviewed studies, 25% of patients withdrew from the studies." The guideline did not refer to buprenorphine when listing weaker opioids. It highlights the lack of long-term studies of the use of opiates in treating patients with osteoarthritis.

Additional information: previous SMC advice

Following a second resubmission, SMC published advice in August 2008: buprenorphine transdermal patches (Butrans®) are not recommended for use within NHS Scotland for the treatment of severe opioid responsive pain conditions, which are not adequately responding to non-opioid analgesics. In the patient population considered in this submission, severe osteoarthritis pain in elderly patients whose pain is not adequately controlled by non-opioid analgesics, or for whom other analgesics are not suitable, buprenorphine transdermal 7-day patch was superior to placebo and similar in efficacy to comparator agents. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

Additional information: comparators

Co-dydramol 10/500, co-codamol 30/500, paracetamol plus codeine, and tramadol tablets.

Additional information: costs

Drug	Dose	Cost (£) per month (28 days)
buprenorphine transdermal patch	**5 to 40 microgram/hour (patch changed weekly)**	**18 to 121**
co-dydramol (10/500 to 30/500)	Up to eight daily	6 up to 28
co-codamol (8/500 to 30/500)	Up to eight daily	7 up to 10
paracetamol plus codeine	1g four times daily plus 30-60mg four times daily	8 to 12
tramadol	100 to 400 mg daily	2 to 7

The prices quoted are from evadis accessed on the 29th September 2008 and BNF edition 56 (September 2008). Doses are for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated a gross drug cost of £819k in year 1, rising to £1.5m by year 5. This was based upon the osteoarthritis patient subgroup with an estimated 5,400 patients in year 1, rising to 9,557 by year 5, representing market shares of 15% and 25% respectively. The manufacturer assumed that patients with inadequate pain control, with contraindications to NSAIDs/ COX- 2 inhibitors or requiring a switch due to side-effects of other 'Step 2' opiod analgesics would be the most likely candidates for treatment with buprenorphine transdermal patches. No net budget impact estimate was presented.

Were buprenorphine transdermal patches to be used for other conditions outside the indication considered in this case, the budget impact would rise accordingly.

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 14 November 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

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