

Resubmission

**buprenorphine transdermal patches 5, 10 and 20 microgram/hour
7-day formulation (BuTrans[®]) No. (234/06)**
Napp Pharmaceuticals Ltd

04 July 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 2nd resubmission

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.

The licence holder has indicated their decision to resubmit.

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.

At the manufacturer's request, the indication under consideration in this second 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.

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% 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 confidence intervals (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.

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 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 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% 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, 2.95) times greater in patients receiving placebo than in patients treated with buprenorphine (p=0.022).

*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.

*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 means that continuous non-oral pain relief over a 7-day period may offer advantages in therapy.

The company suggest that buprenorphine 7-day patches may be used at step 2 of the World Health Organisation 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 can not be considered standard treatment for chronic pain. The robustness of the evidence base is limited and assessment difficult due to the variation in trial design, (different titration methods, background analgesia, lengths of treatment and pain aetiology), significant discontinuation rates and the relatively short duration of the studies, despite this treatment being for a chronic condition.

The robustness of the evidence base is further tested by the restriction in the licensed indication 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, along with two in chronic back pain and one placebo-controlled study in non-malignant pain, all three of which included patients with osteoarthritis pain (ranging from 30-53% of patients included in these studies) and patients 65 years and over. The primary outcome in the comparative osteoarthritis study showed a greater than 2-box reduction in the BS-11 score which is considered clinically relevant.

In the two studies in osteoarthritis it was demonstrated that pain control in the 65 years and over group was as effective as in those patients under 65 years. Unfortunately, there is no information on outcomes for those patients who had osteoarthritis pain and were over 65 years in the back pain and non-malignant pain studies.

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

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis which modelled the effects of buprenorphine transdermal patches once all other active treatment options had been exhausted. This confirmed the results the manufacturer presented in their previous submission: buprenorphine transdermal patches would not be cost effective relative to other active treatment options and should only be considered if patients would otherwise be moving into the no treatment scenario. As a consequence, the manufacturer only considered the comparators of placebo and no analgesia.

The response rate for buprenorphine transdermal patches was taken from the newly available trial of buprenorphine transdermal patches plus paracetamol. The response rate for

placebo was taken from the meta-analysis of the previous submission. The response rate for no analgesia was assumed to be zero, in effect describing the placebo effect within the buprenorphine transdermal patches arm as a real clinical impact which should be valued. Quality of life values were drawn from the newly available trial, based upon EQ-5D responses and the standard social tariff values.

Relative to placebo the cost effectiveness of buprenorphine transdermal patches was estimated to be £11,267 per QALY. Relative to no analgesia the cost effectiveness of buprenorphine transdermal patches was estimated to be £2,497 per QALY.

Weaknesses of the analysis included:

- relying upon the argument used in the previous submission that buprenorphine transdermal patches could be cost effective as a last in line treatment, despite this having already been rejected by the SMC;
- ignoring all clinical effectiveness estimates of other active treatments within the current submission; and;
- including a no-analgesia comparator which in effect values the placebo effect within the buprenorphine transdermal patches as a real effect.
- failure to consider treatment options at the next step in the pain ladder which may be appropriate for this patient group.

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

Summary of patient and public involvement

Patient Interest Group Submission: Pain Concern
Patient Interest Group Submission: Pain Association Scotland.

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: 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)	Up to eight daily	Up to 28
co-codamol (30/500)	Up to eight daily	Up to 17
Paracetamol plus codeine	1g four times daily plus 30-60mg four times daily	10 to 12
tramadol	100 to 400 mg daily	2 to 7

The prices quoted are from evadis accessed on the 6th May 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 within this subgroup.

As the position anticipated within the economics was that buprenorphine transdermal patches would only be used once other active treatment options had been exhausted and patients would otherwise move onto no treatment, no savings reduction in use of other treatments were anticipated.

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

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 **13 June 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/>*