# Scottish Medicines Consortium

## oxycodone prolonged release tablets 5,10,20,40 and 80mg (OxyContin®) No. (197/05)

## Napp Pharmaceuticals Limited

*New indication for the treatment of severe pain requiring the use of a strong opioid*

5th August 2005

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

Oxycodone prolonged release (OxyContin®) is accepted for restricted use within NHS Scotland for the treatment of severe non-malignant pain requiring a strong opioid analgesic

Oxycodone prolonged release is restricted to use in patients in whom controlled release morphine sulphate is ineffective or not tolerated..

Overleaf is the detailed advice on this product.

**Vice Chairman**
**Scottish Medicines Consortium**

**Oxycodone prolonged release tablets 5,10,20,40 and 80mg (OxyContin®)**

## Licensed indication under review

The treatment of severe pain requiring the use of a strong opioid.

## Dosing information under review

Tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements. Opioids are not first line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

## Launch date

May 2004

## Comparator medications

Transdermal fentanyl, transdermal buprenorphine, morphine controlled release

## Cost per treatment period and relevant comparators

| Medicine | Dose | Cost per month (30 days) |
|---|---|---|
| **Oxycodone prolonged release** | **20-40mg 12 hourly** | **£52 - £104** |
| Transdermal fentanyl | 25-50 mcg /hour every 72 hours | £55-£103 |
| Transdermal buprenorphine | 35-52.5mcg/hour for 72 hours | £58- £87 |
| Morphine controlled release | 20-80mg 12 hourly | £8 - £27 |

The prices quoted are from MIMS May 2005. They are not exact comparisons but as close an approximation as possible when applying different conversion factors and with the limited dose flexibility of the patches. Morphine 80mg is equivalent to oxycodone 40mg; transdermal fentanyl '25' is equivalent to 90mg morphine/daily and transdermal buprenorphine '35' is approximately equivalent to 30-60mg morphine/daily.

## Summary of evidence on comparative efficacy

Oxycodone is a semi-synthetic morphine derivative which has affinity for the kappa, mu and delta receptors. It is a full opioid agonist with no antagonist properties. The ratio of the equivalent analgesic dose of morphine to oxycodone is 2:1. Oxycodone prolonged release has been licensed in the UK for moderate to severe cancer pain and post operative pain since 1999 and was granted the licence extension for severe pain requiring treatment with a strong opioid in 2003.

There are 12 studies of oxycodone prolonged release in chronic non-malignant pain in three different pain aetiologies, neuropathic pain, osteoarthritis and chronic low back pain;however, only three of these trials have included an active comparator (either normal release oxycodone or oxycodone with paracetamol) in one trial in osteoarthritis and two trials in chronic low back pain. There are no direct comparisons against other opioid analgesics.

Osteoarthritis

Two of the three trials in patients with osteoarthritis were double-blind, placebo-controlled studies. In a 60 day active comparator study patients with confirmed osteoarthritis and moderate to severe pain despite NSAID use underwent a 30 day open label titration with normal release (NR) oxycodone until pain was stable. Patients were then randomised to oxycodone prolonged release 10-30mg 12 hourly (n=34), oxycodone/paracetamol 5mg/325mg four times daily to a maximum of 12 tablets daily (n=37) or placebo (n=36). Patients continued on stable NSAID therapy throughout the study. Fifty nine of 167 patients discontinued during the titration phase with NR oxycodone (36 due to adverse events, 17 due to ineffective treatment) and 36 patients discontinued during the double-blind phase (20 due to ineffective treatment, 11 due to adverse events). The primary outcome measures were the global pain intensity (GPI) at weeks 6 and 8 (using a categorical scale where 1 = very poor and 5 = excellent) and the difference in global pain intensity at these time points. The global pain intensity scores were significantly reduced in the oxycodone prolonged release and oxycodone/ paracetamol groups compared with placebo at weeks six (mean GPI oxycodone prolonged release 1.41, p = 0.0003 and mean GPI oxycodone/ paracetamol 1.35, p = 0.0001) and eight (mean GPI oxycodone prolonged release 1.59, p=0.0067 and mean GPI oxycodone/ paracetamol 1.46, p=0.0006, respectively). Global pain intensity difference between week four (end of titration) and week eight showed that pain increased significantly in all groups with mean increases of 1.00 ± 0.13 for placebo, 0.44 ± 0.13 for oxycodone prolonged release and 0.49 ± 0.11 for oxycodone/paracetamol. The increase was significantly greater in the placebo group than either oxycodone group (p=0.004). The secondary endpoint of quality of sleep scores showed a significant increase in the oxycodone prolonged release group compared with both other treatments (mean score of 3.61 compared with 3.27 and 2.69 for oxycodone/paracetamol and placebo, respectively). Quality of sleep scores were lower at week eight than week four in all three groups but the decrease was only significant in the placebo group.

Chronic low back pain

Two of the three studies in low back pain included NR oxycodone as the active comparator, the other was placebo-controlled. All were randomised, double-blind studies with titration to pain control. An unpublished comparison in patients with a history of severe chronic back pain of = one month and unresponsive to non-opioid analgesics compared oxycodone prolonged release 10-40mg 12 hourly (n=129) with NR oxycodone liquid 5mg/5ml 6 hourly in doses of 20-80mg daily (n=116). Patients were randomised, then allowed to titrate their dose to optimum pain control over the following 20 days, then entered into the 20 day assessment phase. The treatment differences in mean pain scores over the last seven days of the assessment phase were within the limits defined for equivalence. The secondary endpoints of sleep disturbance and quality of sleep were improved in both groups with the median number of nights woken because of pain reduced from seven out of seven to two or three out of seven nights at the end of the assessment. Quality of sleep also improved with the number of patients randomised to oxycodone prolonged release reporting poor or very poor sleep reduced from 79% at baseline to 20% at the end of the assessment. The one published comparison, randomised 57 patients with moderate to severe low back pain to open label titration with oxycodone prolonged release 10-40mg 12 hourly (n=30) or NR oxycodone 5mg four times daily in doses of 20-80mg daily. Patients who achieved stable analgesia within 10 days were then randomised to a double-blind crossover assessment of 4-7 days for each

treatment. At the end of each treatment phase the overall pain intensity scores were low in both groups; 1.2±0.1 and 1.1±0.1 for the prolonged release and normal release formulations, respectively.

Long term studies

Three open long term studies of one to three years duration in a range of different pain aetiologies enrolled a total of 587 patients. All three trials measured the acceptability of treatment as a primary outcome measure and showed an early increase in acceptability scores which was maintained throughout all trial periods (except for one measurement at one time point). Two trials measured global pain intensity scores as a primary outcome and showed an initial decrease which was mostly maintained for 12 and 18 months respectively. In one trial the Short Form 36 Health Survey Scale, a generic health-related quality of life measurement with nine different outcome measures, was a primary outcome measure and showed an early improvement but this was followed by a trend back to levels below baseline at month 36.

## Summary of evidence on comparative safety

No new safety concerns became apparent during the studies of non-malignant pain. The adverse effect profile of oxycodone prolonged release is similar to that of other strong opioids.

## Summary of clinical effectiveness issues

There is a paucity of comparative evidence for the use of opioids in non-malignant chronic pain of all aetiologies. Twelve clinical studies were submitted by the company but only three of these involved an active comparator which was the normal release formulation of oxycodone or a combination of oxycodone with paracetamol. There was no significant difference in the reduction in pain intensity scores or tolerability recorded for the different oxycodone formulations. The licensed indication for oxycodone prolonged release is for severe pain requiring a strong opioid but most of the trials included patients with moderate as well as severe pain. Three trials were less than one month's duration and three were the minimum one month duration. The different methodologies and protocols used in the trials made assessment difficult. These involved different pain aetiologies, fixed dose, titration to pain control, titration before randomisation, titration after randomisation, crossover (no washout period at crossover), different duration, rescue medication allowed and not allowed, some patients previously treated with an opioid. Withdrawal due to both adverse effects and ineffective treatment showed wide variation and in one trial was greater than 50%. The prevalence of chronic pain in the community is relatively high and yet many of the trials recruited only around 100 patients, although the open label long term trials were larger.

## Summary of comparative health economic evidence

A cost-utility analysis using a Markov chain model to estimate treatment duration based on an estimate of long term treatment failure rate was used to assess the most cost-effective sequencing of oxycodone prolonged release, morphine controlled release and transdermal fentanyl in the treatment of chronic non-malignant pain. The main measure of effectiveness was pain scores from clinical trials, which were then converted to QALYs using an algorithm to map the pain scores to equivalent European Quality of Life Measure (EQ-5D) utility scores. The conclusion was that all the products could be considered cost-effective (with a cost per QALY for all under £10,000) compared to supportive care, but that optimal cost-effectiveness

would be obtained by positioning oxycodone prolonged release as second line to morphine controlled release, but ahead of transdermal fentanyl.

The main difference between the products was in cost. Mean daily drug dose for each of the three treatments was derived from an analysis of the GP Research Database and combined with costs of treating adverse events (constipation and nausea/vomiting). This demonstrated a higher average cost for oxycodone prolonged release compared to morphine controlled release and lower costs than transdermal fentanyl.

A weakness in the economic case submitted by the manufacturer was in the clinical evidence used. In the absence of comparative trials for oxycodone prolonged release versus morphine controlled release or transdermal fentanyl in non-malignant pain, meta-analysis of randomised trials was performed for pain scores and adverse events, pain scores were then converted to utility estimates for the three products. However, in order to carry out the indirect comparison of cost-effectiveness across all three products, trials of patients with cancer pain were also included, which was broader than the licence extension covered by the submission. In addition, utility outcomes linked to pain scores were included but not any attempt to measure disutility associated with adverse events. Hence, the relative effectiveness of oxycodone in only those patients with non-malignant pain was not clearly demonstrated. However, accepting that the benefits of oxycodone prolonged release in analgesia are likely to be similar in patients with different types of pain (although the impact on quality of life may vary considerably), the economic case submitted supports relative cost-effectiveness.

## Budget impact

Oxycodone prolonged release for chronic non-malignant pain has been licensed since October 2003. Hence, it was estimated that had already been used in 750 patients with chronic non-malignant pain conditions in 2004. The budget estimate for 2005 was a cost of £293,000 (for 885 patients), rising to £336,000 in 2006 and up to £502,000 (for 1,500 patients) by 2009, based on a combination of 9% growth per annum in numbers with chronic pain receiving treatment and a 1% growth per annum in market share for oxycodone prolonged release (at the expense of fentanyl).

## Guidelines and protocols

Recommendations for the appropriate use of opioids for persistent non-cancer pain, a consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists, March 2004.

## Additional information

ReceRecent publications have undertaken dosing surveys in the United States for oxycodone prolonged release. These found that for many patients pain relief does not last the full twelve hours, resulting in these patients taking their medication more frequently.

In December 2002 the Scottish Medicines Consortium (SMC) issued advice regarding fentanyl transdermal patches (Durogesic®) advising that transdermal fentanyl should be considered as a second-line alternative for patients with intractable pain due to non-malignant conditions. It should be reserved for patients whose pain has initially been controlled by oral means, the pain being relatively stable. Its use should focus on such patients who have difficulty swallowing or have problems with opiate induced constipation. NB: Transdermal patches are significantly more expensive than oral therapy.

***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 15 July 2005.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.*

*References*


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*Recommendations for the appropriate use of opioids for persistent non-cancer pain. A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists, March 2004.*

*Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain. Committee for Proprietary Medicinal Products. The European Agency for the Evaluation of Medicinal Products. http://www.emea.eu.int*

*Clinical Study Report OC97-0702*

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