

oxycodone/naloxone 10mg/5mg and 20mg/10mg prolonged release tablets (Targinact®) **No. (541/09)**

Napp Pharmaceuticals Ltd

06 February 2009

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/naloxone prolonged release tablets (Targinact®) are not recommended for use within NHS Scotland for the treatment of severe pain which can be adequately managed only with opioid analgesics.

The addition of naloxone to oxycodone did not impair analgesia and improved bowel function when patients were not receiving regular laxative therapy. However the clinical benefit in patients receiving regular laxative therapy is uncertain and the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman
Scottish Medicines Consortium**

Indication

Severe pain, which can be adequately managed only with opioid analgesics.

The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

Dosing information

The usual starting dose for opioid-naïve patients is 10mg/5mg oxycodone/naloxone every 12 hours. For patients requiring higher doses 20mg/10mg oxycodone/naloxone is recommended. The maximum daily dose is limited to 40mg/20mg. Patients requiring higher doses should be administered supplemental prolonged release oxycodone 12-hourly (within the maximum daily dose of 400mg oxycodone prolonged release).

Product availability date

26 January 2009

Summary of evidence on comparative efficacy

Oxycodone is an opioid analgesic established in the management of severe pain. Constipation is one of the most common adverse events associated with opioid therapy through the action of the opioid on mu receptors in the gastrointestinal tract resulting in decreased gastrointestinal motility and peristalsis, decreased secretions and increased intestinal fluid absorption. Naloxone is an opioid antagonist which, when administered orally, has poor systemic availability, resulting in local antagonism of the effects of oxycodone in the gastrointestinal tract.

The company has suggested that the combination is expected to be used as an alternative to opioids for patients with severe chronic non-malignant pain who have, or are at risk of, opioid-induced constipation.

Three studies have evaluated the effects of the oxycodone/naloxone combination in patients with moderate to severe, chronic, non-malignant pain. Only two of these studies have been published. A double-blind double-dummy study was designed to assess the analgesic efficacy of oxycodone/naloxone compared with oxycodone prolonged-release and placebo. Eligible patients were aged ≥ 18 years with a history of moderate to severe chronic non-malignant lower back pain which was adequately managed with daily opioids (equivalent to $>10\text{mg}$ or $<40\text{mg}$ oxycodone daily) for at least two weeks before enrolment. Patients entered a screening period with opioid taper, followed by a run-in period of opioid titration with immediate-release oxycodone to a target dose of 20mg or 40mg daily. Patients who achieved adequate analgesia were randomised to oxycodone/naloxone 10mg/5mg or 20mg/10mg every 12 hours ($n=154$), oxycodone prolonged release 10mg or 20mg every 12 hours ($n=151$) or placebo ($n=158$) for a 12-week double-blind phase. Patients were permitted to receive immediate release oxycodone for breakthrough pain. The primary endpoint was the time from the initial dose of study medication to recurring pain events defined as inadequate pain control ("average pain over 24 hours" or "pain right now" measuring ≥ 5 on the pain intensity scale [0 to 10] and rescue medication at least twice per day) for two consecutive days.

The mean time to first pain event was significantly longer in the active groups compared with placebo. There were no significant differences in the times to each pain event between the

oxycodone/naloxone group and the prolonged release oxycodone group. The risk of experiencing a pain event was 42% lower in the oxycodone/naloxone group than in the placebo group (hazard ratio (HR) 0.58 (95% confidence interval (CI): 0.46 to 0.74) and 6% higher with oxycodone/naloxone than with oxycodone prolonged-release (HR 1.06 (95% CI: 0.81 to 1.39). Equivalence of analgesic efficacy was regarded as demonstrated.

A second study enrolled 322 patients aged ≥ 18 years with moderate to severe chronic non-malignant pain receiving regular opioid therapy (oxycodone equivalent of ≥ 20 mg/day and ≤ 50 mg/day) and constipation (defined as $<$ three complete spontaneous bowel movements (CSBM) during the last 7 days). Eligible patients were randomised to oxycodone/naloxone or prolonged release oxycodone tablets every 12 hours. The primary efficacy measure was patients' assessment of their symptoms of constipation using the Bowel Function Index (BFI), a scale which assesses each of ease of defaecation, feeling of incomplete evacuation and personal judgment of constipation on a 0-100 scale and averages the scores from these three domains to produce the BFI.

During the first 4 weeks of the double-blind phase, the BFI score (using last observation carried forward) reduced from 62 to 35 in the oxycodone/naloxone group compared with 61 to 52 in the oxycodone prolonged release group: difference -15 (95% CI: -18 to -12) at week 4. Brief results of exploratory analyses reported in the Summary of Product Characteristics, indicate that patients treated with oxycodone/naloxone had on average one extra CSBM during week 4 compared to patients treated with oxycodone prolonged-release (3.5 versus 2.4 respectively). The use of 'rescue' laxatives was significantly lower in the oxycodone/naloxone group (31% versus 55% respectively).

The third study, not yet published, was of similar design to the study described above but used doses of oxycodone/naloxone in excess of those licensed and will not be discussed further.

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

Summary of evidence on comparative safety

The majority of reported adverse events in the studies were mild to moderate in severity. Those most frequently reported were gastrointestinal in nature and were broadly similar between the oxycodone/naloxone and oxycodone treatment groups. The incidence of severe adverse events was low. During the 12-week double-blind phases the addition of naloxone to oxycodone did not appear to produce symptoms of opioid withdrawal when given at the licensed dose.

Summary of clinical effectiveness issues

The studies with oxycodone/naloxone were conducted in patients with moderate to severe chronic non-malignant pain although the combination has been licensed for the treatment of severe pain. Data on the treatment of pain in patients with cancer were not presented in the company submission.

The duration of double-blind treatment in the studies was limited to 12 weeks and the primary outcome of constipation in the second study was assessed at 4 weeks. Therefore longer term controlled data are lacking which may be relevant if the combination product is to be used in the management of chronic pain. The effects on analgesia and bowel function were assessed and recorded in a diary by the patients in the studies and are therefore

subjective outcomes. A change of at least 12 points in the BFI score (on a scale of 0 to 100) is considered clinically relevant. During the first 4 weeks of the study, the difference between the mean BFI scores of the oxycodone/naloxone and prolonged-release oxycodone groups was 15.

In the second study, which used BFI as the primary endpoint, bisacodyl was permitted and it is not clear how this affected the results. Patients were converted to a standard laxative regimen using oral bisacodyl. In practice, opioid-induced constipation is usually managed with regular prophylactic use of a stimulant laxative, such as bisacodyl, plus a faecal softener to prevent constipation. The effect of using oxycodone/naloxone rather than oxycodone alone in patients managed in this way is uncertain.

The maximum recommended dose for the oxycodone/naloxone combination is 40mg/20mg daily. For patients requiring higher analgesic doses, supplemental prolonged-release oxycodone is recommended (to a maximum of 400mg daily) but this may impair the effect of naloxone on bowel function..

The systemic absorption of naloxone is reported to be higher in patients with renal and hepatic impairment which may be a disadvantage in a potentially elderly population. In addition, while opioids are thought to cause constipation by acting on mu opioid receptors in the gastrointestinal tract, there may be other contributory mechanisms.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility decision tree model over a one year time horizon. This compared laxative use associated with the use of oxycodone/naloxone with that of oxycodone prolonged-release. Clinical effectiveness in terms of both the average daily dose and average rates of laxative use were taken from one of the randomised controlled trials comparing oxycodone/naloxone with oxycodone prolonged release. The balance between different laxatives and other resource use was estimated from a manufacturer-commissioned survey of GPs, these being valued using standard sources.

Quality of life values for the three health states of the model were derived from three different sources: a study among neuropathic pain patients with failed back surgery syndrome for those receiving opioid treatment but not requiring laxatives; a survey among 175 UK GPs using the EQ-5D visual analogue scale (VAS) for those receiving both opioid treatment and laxatives; and standardised age weighted utilities for patients requiring neither analgesia nor laxatives.

The results showed an additional opioid drug cost of £118 from the use of oxycodone/naloxone but savings from reduced laxative use and other resource use reduced this to a net total cost of £93. Oxycodone/naloxone was anticipated to result in an additional 0.02 QALYs relative to oxycodone prolonged-release, and as a consequence the cost effectiveness was estimated as £4,712 per QALY.

An additional comparison was made with modified release morphine. This anticipated that laxative use rates would be as for oxycodone prolonged-release but that the treatment duration would be 310 days of the year as compared with 258 days for the oxycodone containing regimes. A dose conversion of 2:1 for morphine:oxycodone prolonged release was assumed. The other resource use for those requiring laxatives as identified through the GP survey also anticipated a higher cost for those receiving morphine.

This analysis resulted in an additional opioid drug cost of £374 from the use of oxycodone/naloxone and savings from reduced laxative use and other resource use reduced this to a net cost of £336. Oxycodone/naloxone was anticipated to result in an additional 0.06 QALYs relative to morphine, and as a consequence the cost-effectiveness was estimated as £5,383 per QALY.

Weaknesses of the analysis included:

- an unusual model structure, with health states being defined in terms of use of laxatives rather than the degree of constipation;
- a poor estimation of utilities that took values from disparate sources which were not obviously comparable with one another;
- initial failure to incorporate the SF-36 quality of life data collected within the studies to estimate utilities. The manufacturer subsequently provided sensitivity analysis using these data which suggested a cost per QALY of £6184 versus oxycodone prolonged release or £22,254 versus morphine. It should be noted however that further detail would be required in order to rely on these new estimates;
- the utility value for receiving laxatives being based upon a GP survey which asked about the impact of constipation on quality of life rather than the impact of treated constipation;
- laxative use, regardless of its effectiveness, being estimated to reduce quality of life by around a quarter in the base case which seems extreme. However, threshold analysis indicated that the level of disutility could be reduced to fairly low levels and the ICER still remain within acceptable limits;
- a greater duration of required treatment for morphine which may have been biased. When treatment duration for morphine and oxycodone/naloxone were equalised at 258 days, the ICER increased to £15,483. The results were sensitive to this assumption as the ICER increased to £30k if treatment duration of morphine fell to 243 days;

Given these weaknesses, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Pain Association Scotland.

Additional information: guidelines and protocols

In February 2008, the National Institute for Health and Clinical Excellence (NICE) 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 disease. 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, the British Society for Rheumatology published its guidelines for the integrated management of musculoskeletal pain symptoms. The guidelines cover pain symptom management for all types of arthritis, not just osteoarthritis. The guidelines initially recommend the use of regular paracetamol and then the addition of prescription doses of

codeine if paracetamol alone is insufficient followed by replacing codeine with meptazinol or nefopam or tramadol. Only after this, do the guidelines recommend the use of low dose morphine sulphate or equivalent (e.g. oxycodone or buprenorphine patch).

Additional information: comparators

Other opioid analgesics including controlled release morphine, prolonged release oxycodone, transdermal fentanyl and transdermal buprenorphine with or without laxative therapy.

Cost of relevant comparators

Drug	Dose regimen	Cost per 28 days (£)
Targinact	10mg/5mg to 20mg/10mg every 12 hours	35 to 70
Opioids		
Buprenorphine transdermal patches (Butrans®)*	5 to 40 micrograms/hour every 7 days	18 to 121
Oxycodone prolonged release tablets	10 to 20mg every 12 hours	26 to 53
Buprenorphine transdermal patches (Transtec®)*	35 to 52.5 micrograms/hour every 4 days	29 to 44
Fentanyl transdermal patches	12 to 25 microgram/hour every 3 days	27 to 38
Morphine controlled release tablets	20 to 40mg every 12 hours	7.09 to 12
Laxatives		
Movicol	1 to 3 sachets daily	6.48 to 19
Docusate sodium	up to 500mg daily	up to 11
Lactulose	15ml twice daily	4.87
Bisacodyl	5 to 10mg daily	1.75 to 3.50
Senna	2 to 4 tablets daily	1.39 to 2.78

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 1 December 08. Morphine 80mg is equivalent to oxycodone 40mg; transdermal fentanyl 25 is equivalent to morphine 90mg/day.

*Buprenorphine quoted for licensed dosage range: both products are not recommended for use by SMC.

Additional information: budget impact

The manufacturer estimated a gross drug cost of £131k in year 1, rising to £441k by year 5. Given drug costs offsets from reduced use of oxycodone prolonged release this resulted in a net drug cost of £30k in year 1, rising to £100k by year 5. The manufacturer also estimated savings from reduced laxative use of £6k in year 1 rising to £21k in year 5.

This was based upon 3,500 patients currently receiving oxycodone prolonged release at a dose of less than 40mg per day, among whom it was estimated that 41% (1,437 patients) would experience constipation. Market share was estimated as being 17.6% (253 patients) in

year 1 rising to 59.2% (850 patients) by year 5. Comments from SMC experts suggested that the budget impact estimated by the manufacturer may be an underestimate.

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 16 January 2009.

Drug prices are those available at the time the papers were published 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/>*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Vondrackova D, Leyendecker P, Meissner W et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain. In press 2008. doi:10.1016/j.jpain.2008.06.014

Ahmedzai SH, Boland J. Constipation in people prescribed opioids. BMJ Clin Evid 2007;12:2407