PUBLIC SUMMARY DOCUMENT
Product: OXYCODONE HYDROCHLORIDE and NALOXONE HYDROCHLORIDE DIHYDRATE, tablets, 5 mg-2.5 mg, 10 mg-5 mg, 20 mg-10 mg and 40 mg-20 mg (controlled release), Targin®
Sponsor: Mundipharma Pty Ltd.
Date of PBAC Consideration: July 2010

1. Purpose of Application
The submission sought a restricted benefit listing for patients with chronic severe disabling pain not responding to non-narcotic analgesics.

2. Background
This combination drug had not previously been considered by the PBAC.

3. Registration Status
Oxycodone hydrochloride with naloxone hydrochloride dihydrate was TGA registered on 12 May 2010 for the management of moderate to severe pain unresponsive to non-narcotic analgesics. The naloxone component in a fixed combination with oxycodone is indicated for the prophylaxis of opioid-induced constipation.

4. Listing Requested and PBAC's View
Restricted benefit
Chronic severe disabling pain not responding to non-narcotic analgesics.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy
Chronic pain occurs in up to 70% of patients with advanced cancer and in approximately 65% of patients suffering from terminal non-malignant disease. Opioids are the current mainstay of pain management for patients with moderate-to-severe cancer pain and are increasingly being used for the treatment of chronic non-cancer pain. Opioid-induced constipation is the most frequently reported side effect which may be treated prophylactically with laxatives.

Oxycodone hydrochloride with naloxone hydrochloride dihydrate could provide an alternative pain management therapy to opioids alone or in conjunction with prophylactic laxatives. It may also potentially reduce the risk of intravenous or intranasal misuse by individuals dependent on opioid agonists such as heroin, morphine or methadone, as oxycodone hydrochloride with naloxone hydrochloride dihydrate tablets are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone.

6. Comparator
The submission nominated oxycodone controlled release as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented three randomised trials comparing oxycodone/naloxone with oxycodone alone in patients with moderate or severe pain (OXN3001, OXN3006 and OXN3401). Two supporting non-randomised trials in patients with cancer-related pain and in palliative care are also presented (OXN9002 and OXN9502).

These trials had been published at the time of the submission as shown in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
OXN3001 Simpson K, et al	Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain.	Curr Med Res Opin 2008 24(12): 3503-3521
OXN3006 Lowenstein O, et al	Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: A randomised controlled trial.	Expert Opin Pharmacother 2009 10(4): 531-543
OXN3401 Vondrackova D, 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 2008 9(12): 1144-1154.
Mueller-Lissner S, et al	Oral prolonged-release oxycodone/naloxone combination reduces opioid-induced bowel dysfunction in chronic pain patients (poster and abstract)	Pain Practice 2007 7: 57
Supplementary non-randomised trials		
OXN9002 Grunert S, et al	Treatment of patients with strong pain due to degenerative spinal disease.	Eur J Pain 2009 13(1): S136
Hesselbarth S, et al	Strong analgesic efficacy and superior tolerability of oxycodone/naloxone prolonged-release tablets in patients with pain due to osteoarthritis.	Eur J Pain 2009 13(1): S133
Nolte T	Prolonged-release oxycodone/naloxone is effective and safe in clinical use.	Onkologie 2008 31(Suppl 1): 1-211.
Nolte T, Schmidt T (2009)	Prolonged-release oxycodone/naloxone is very effective and tolerable in treatment of cancer pain.	Poster S299, 11th Congress of EAPC. Vienna, Austria.
Nolte T, Schmidt T (2008)	Prolonged-release oxycodone/naloxone is effective and safe in cancer pain.	Poster PH066 IASP 12th World Congress on Pain. Glasgow, Scotland.
Schutter U, Meyer C (2009a)	Efficacy and tolerability of prolonged release oxycodone/naloxone.	Eur J Pain 2009 13(1): S208

Schutter U, Meyer C (2009b)	Treatment of moderate to severe pain of opioid-naïve patients with the combination of prolonged-release (PR) oxycodone and PR naloxone.	Poster S307 at 11th Congress of EAPC. Vienna, Austria.
OXN9502		
Clemens KE, et al (2009a)	Analgesic efficacy and improved bowel function during pain therapy with a combination of oxycodone/naloxone prolonged-release tablets in geriatric patients.	Abstract number A118-0019-00629, World Institute of Pain. New York
Clemens KE, et al (2009b)	Bowel function during therapy with a combination of oxycodone/naloxone prolonged-release tablets in geriatric patients.	Poster F317, 11th Congress of EAPC. Vienna, Austria.
Clemens KE, Et al (2009c)	Bowel function during therapy with oxycodone/naloxone prolonged release tablets in geriatric and palliative care patients.	Eur J Pain 2009 13(1): S210

8. Results of Trials

The Bowel Function Index (BFI) was the primary outcome measure in two of the three comparative trials (OXN3001, OXN3006) which were designed primarily to assess bowel function. Study OXN3401 was a pain study in which BFI was an exploratory outcome measure only. BFI was compared using a meta-analysis across the three clinical trials.

The PBAC noted that while the validity of the BFI seemed reasonable, the measure was developed specifically for this product and has not been tested in other contexts.

BFI results from the direct randomised trials are presented in the table below.

Table 1: Results of Bowel Function Index at Week 4 across the direct randomised trials

Trial ID	Oxycodone and Naloxone, Mean BFI (SD)	Oxycodone, Mean BFI (SD)	Mean Difference (95% CI)
OXN3001	34.9 (25.8) n=158	51.6 (26.78) n=158	-16.70 (-22.50,-10.90)
OXN3006	40.94 (27.38) n=130	53.27 (23.86) n=135	-12.33 (-18.52,-6.14)
OXN3401	20.3 (22.4) n=141	25 (22.9) n=138	-4.70 (-10.02,0.62)
Pooled result	N=429	N=431	-11.15 (-18.31,-3.99)

In all three trials, BFI at week 4 was lower in the oxycodone and naloxone group. The difference was statistically significant in the two studies that used BFI to measure the primary study outcome. Controlling for baseline BFI did not impact on this conclusion.

At 12 weeks, the reduction in BFI was higher in the oxycodone/naloxone group than in the oxycodone group. Sub-group analysis suggested that this applied except for patients not constipated at baseline.

The PBAC noted that in trials OXN3001 and OXN3006, patients were included on the basis of constipation. Hence the results may not be applicable to all patients treated with oxycodone.

For PBAC's view on these results, see Recommendation and Reasons.

The PBAC noted the evidence suggested adverse events were comparable between oxycodone/naloxone and oxycodone alone. Constipation was included as an adverse event,

but did not show a statistically significant difference between oxycodone/naloxone and oxycodone alone. However, this did not contradict the primary outcome because, as patients in OXN3001 and OXN3006 were all constipated at baseline, the adverse event in these groups was defined as a worsening of constipation. Thus, those in the oxycodone/naloxone group had reduced levels of constipation while those in the oxycodone group had steady levels of constipation (which would not be identified as an adverse event).

9. Clinical Claim

The submission described oxycodone/naloxone as superior in terms of comparative effectiveness (in terms of bowel function *only*) and equivalent in terms of comparative safety over oxycodone alone.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped modelled economic evaluation with a 1 year time horizon was presented. The model contained two regimens (oxycodone/naloxone and oxycodone), with or without prophylactic laxative use. Patients either become constipated or not constipated. Probabilities (between treatment groups) were determined from the clinical trials OXN3001, OXN3006, OXN3401 and a survey of medical practitioners.

Utility values were assigned to the following health states: constipated and not constipated; associated complications; and adjustments for medication alteration. Measuring the time spent in each over the course of the model produced the incremental number of quality adjusted life years (QALY) attributable to oxycodone/naloxone and oxycodone. This was the primary health outcome of the economic evaluation. Costs of medication, opioid induced constipation (OIC) treatments and complications were approximated and attached to health states. These were summed then used with the health outcome to produce an incremental cost per QALY gained in the base case of between $15,000 and $45,000.

The key drivers of the model were the treatment effect of oxycodone/naloxone in comparison to oxycodone, and the pharmaceutical cost of oxycodone/naloxone.

The PBAC noted a sensitivity analysis had been undertaken during the Evaluation to respecify the base case to incorporate the effect of laxatives on OIC. Depending on the scenario, this produced ICERs in the range of $45,000 to $105,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

According to baseline estimates of net drug costs to the PBS, the submission estimated the financial cost per year to the PBS to be less than $10 million in Year 5. Subtracting the submission's estimated savings due to expected reduction in abuse rates reduced the net cost to the PBS. Subtracting estimated MBS savings through reduced cost of OIC diagnosis and treatment, resulted in a net cost to the Government health budget of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC considered that oxycodone alone was not the appropriate comparator as there was

evidence suggesting a significant proportion of patients were likely to receive prophylactic laxatives, consistent with current clinical guidelines, particularly patients with chronic pain on long term opioid therapy. Therefore, the Committee considered the more appropriate comparator was oxycodone plus prophylactic laxatives. The PBAC agreed with the ESC that if oxycodone plus prophylactic laxatives was the comparator the relative effectiveness of oxycodone and naloxone in terms of constipation and pain would possibly be lower as it would be expected that the comparator would perform better in terms of bowel function.

The primary outcome measure in trials OXN3001 and OXN3006 was bowel function index (BFI). BFI was an exploratory outcome measure in trial OXN3401. The PBAC noted that the pooled meta-analysis of the three trials at week 4 and week 12 showed borderline clinical significance with mean differences of -11.5 and -11.86 respectively. However, the minimum clinically important difference was defined as a change of greater than 12 points. In a further sub-group analysis, based on whether patients received laxatives during the study and whether they were constipated at baseline, there was no statistically significant difference between oxycodone/naloxone and oxycodone, at 4 weeks or 12 weeks in the group that was not constipated at baseline. However, the PBAC acknowledged that this was a small sub-group.

The PBAC considered that the populations in the key clinical trials were not representative of the likely Australian population, or the requested listing, particularly in respect to the exclusion of palliative care and oncology patients and prophylactic laxative use. The PBAC considered the restriction of laxative use to stimulant alone, in two of three trials, was not representative of the different types of laxatives which could be used. Therefore the effectiveness of laxatives was likely underestimated, which would bias against oxycodone alone as laxative use was more prevalent in this group.

The PBAC considered that the clinical claim that oxycodone/naloxone is superior in terms of comparative effectiveness (in terms of bowel function only) and equivalent in terms of comparative safety over oxycodone alone was reasonable given the evidence. However, the impact of using oxycodone and prophylactic laxatives as the comparator could not be determined from the evidence.

The PBAC considered that the timeframe of the economic model of 1 year was inappropriate for patients who have non-malignant pain as treatment duration in clinical practice would likely be longer.

The PBAC noted that the economic model was highly sensitive to the risk ratio derived from the randomised controlled trials and agreed with the ESC that a major flaw with the model was that BFI scores, which were the primary outcome of two of the three trials, were not used as the primary clinical input. The submission inappropriately used rescue medication laxative use (defined as the relative risk ratio), as a proxy for opioid induced constipation (OIC) to inform the model. The risk ratio was calculated from the meta-analysis of the three trials, OXN3001, OXN3006 and OXN3401. As BFI scores were not incorporated into the risk ratio calculation, the calculation of the relative risk ratio was considered to be highly uncertain. The model assumed a risk ratio response of 1.5 which the Committee noted was the highest possible risk ratio that could have been chosen from the range of options available, meaning that patients have a probability of 1.5 of using rescue laxatives with oxycodone, when compared with oxycodone and naloxone and therefore a probability of 1.5

of developing OIC. The PBAC considered that the conclusion used in the model that the development of OIC occurred at the same rate irrespective of prophylactic laxative use was not appropriate as the model was shown to be sensitive to lower levels of OIC with laxative use which favoured oxycodone.

The PBAC considered that the base case of between $15,000 and $45,000 per QALY gained was highly uncertain given the assumption that individuals who take prophylactic laxatives have the same probability of OIC as those who do not take laxatives and that all complications of OIC will occur. When the base case was respecified, taking into account the proportion of individuals taking laxatives (derived by multiplying the ratio of OIC with laxatives/no laxatives by the probability of OIC, the ICER was in the range of $45,000 to $105,000 per QALY. The PBAC noted that a further multivariate probabilistic sensitivity analysis undertaken during the evaluation produced an ICER of greater than $200,000 per QALY.

The PBAC considered that the calculated average daily dosage (ADD) of 38.71mg, which was estimated based on current Australian IMS data of oxycodone, with the exclusion of all patients utilizing 80 mg tablets, was an underestimate. The Committee considered it possible that patients requiring high doses of pain relief could exceed the 80 mg ceiling dose of oxycodone and naloxone with the balance of their daily dose being from oxycodone alone. Therefore, it would be appropriate to include a proportion of 80 mg prescriptions in the ADD calculations. The PBAC noted that the pooled trial data suggested an ADD of 48.01mg and that adjusted Australian IMS data, which included all 80 mg patients, suggested an ADD of 52.28 mg. Further, the extension study OXN 3401S, although not comparative, showed that the average daily dose was likely to increase over time.

The PBAC considered that the costs and disutility effects may potentially have been over estimated due to the assumption in the model that on average all patients who develop OIC develop at least one complication, however it was noted that the GP survey found that over 25% of patients had no complications. The PBAC questioned the reliability of the data used in the model as it was derived from a clinician survey which had a poor response rate and relied on recall rather than an audit of practice. The PBAC agreed that use of BEACH data may have been an alternative and better source of data to determine GP practice.

The PBAC agreed with the DUSC that the submission's estimated uptake rate was a likely underestimate and that a more realistic baseline estimate, which would include switching from other opioid treatments, would be higher based on the GP estimates from the practitioner survey. The PBAC noted that the submission did not include 20mg under-copayment oxycodone CR scripts and therefore considered that the submission's estimates of the number of prescriptions/patient/year were uncertain. The PBAC also considered that the potential for reduction in illicit drug use was not based on evidence and hence estimated savings to the PBS were also uncertain.

Therefore the PBAC rejected the submission on the basis of an uncertain and high cost-effectiveness ratio.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.