Summary

- A fixed dose oral prolonged release (PR) oxycodone and prolonged release (PR) naloxone combination tablet is a new preparation for the treatment of severe pain which can only be adequately managed by opioid analgesics.
- Naloxone has been added to counteract opioid induced constipation. The bioavailability of naloxone after oral administration is <3% because of first pass metabolism. A clinically relevant systemic effect, particularly the reversal of analgesia in the spinal cord and brain, is unlikely.
- Based on safety and efficacy data from phase II trials, the optimal PR oxycodone/PR naloxone ratio is 2:1. The PR oxycodone and PR naloxone combination tablet is available in 2 strengths – 20mg oxycodone + 10mg naloxone (20mg/10mg) and 10mg oxycodone + 5mg naloxone (10mg/5mg). The PR tablet should be given every 12 hours.
- Three phase III, randomised, double blind, parallel group, multicentre, 12 week trials in over 1,000 patients have assessed the analgesic efficacy, safety and effect on symptoms of constipation secondary to opioid treatment of the PR oxycodone/PR naloxone against placebo and PR oxycodone. Each of these trials had 12 month extension phases, two of which have been completed but not yet published.
- Patients in the trials were mainly on long term opioids for back pain, osteoarthritic pain, postoperative pain (phase II only) and neuropathic pain. Patients with cancer pain were excluded from the phase III trials.
- The trials showed that the addition of PR naloxone does not affect the analgesic efficacy of PR oxycodone; there was a clinically relevant improvement in bowel function with the PR oxycodone/PR naloxone combination compared to PR oxycodone monotherapy and the incidence of adverse effects was comparable between the different treatment groups.
- The addition of PR naloxone to PR oxycodone does not completely negate the need for laxatives, in a long term clinical trial about 10% of patients still required regular additional laxatives.
Summary cont.

- Currently there is very little long term data available. A 12 month open label extension to a phase III trial showed that patient scores for average pain over the last 24 hours, pain intensity, and interference of pain with sleep and activities remained low and stable. The mean daily dose of PR oxycodone/PR naloxone increased which possibly indicates a natural progression of the underlying chronic pain condition or increasing drug tolerance. Use of rescue medication was low.
- Patient assessment of the PR oxycodone/PR naloxone combination is that it is effective and well tolerated.
- The safety and efficacy of the PR oxycodone/PR naloxone product has not been established in cancer patients and/or patients with liver metastasis in randomised clinical trials. There is data on use in cancer patients from an observational study.
- The cost of the PR oxycodone/PR naloxone preparation is £35.11 and £70.22 for the 10/5mg and 20/10mg tablets in packs of 56 respectively. PR oxycodone plus concomitant laxatives is more expensive than PR morphine plus concomitant laxatives.

A fixed dose prolonged release (PR) oxycodone and prolonged release (PR) naloxone combination tablet is a new preparation for the treatment of severe pain which can only be adequately managed with opioid analgesics. Naloxone has been added to counteract opioid induced constipation. It is the first PR agonist and antagonist combination licensed for pain management in the UK.

This briefing document aims to evaluate the information currently available on the fixed dose oxycodone and naloxone combination tablet (Targinact, Napp) and view its place in therapy of severe, chronic pain.

Background

Large scale surveys done in Europe and Australia have shown that approximately 20% of the adult population has severe, persistent pain, which in many people is not related to cancer. The pain is not well controlled and seriously affects the quality of social and working lives. (1) Applying these figures to the English adult population, suggests that persistent, severe, non-cancer pain affects up to 8 million people.

Opioids are effective in some patients for persistent, severe, non-cancer pain. For the treatment of moderate or moderate to severe opioid-sensitive pain, codeine is the traditional choice. More potent opioids such as morphine and oxycodone are mainly used in the treatment of severe acute non-malignant pain and cancer pain. Their use in chronic non-malignant pain has been questioned because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. (2-4)

In usual doses one of the commonest adverse effects of opioid analgesics is constipation. Unlike other adverse effects, tolerance does not develop with long-term use. (2, 3) The British National Formulary (BNF) states that constipation is almost invariable after administration of an opioid. The BNF highlights that codeine is effective for the relief of mild to moderate pain but is too constipating for long term use. Constipation should be prevented if possible by the regular administration of laxatives e.g. bulk forming laxatives - ispaghula husk; osmotic laxatives - lactulose solution, macrogols and stimulant laxatives - bisacodyl, senna, docusate sodium. (5)
Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is normally used intravenously to reverse the effects of acute opioid overdose, such as respiratory depression. In patients receiving longer-term opioids, naloxone has been reported to alleviate some of their adverse effects without loss of therapeutic efficacy. In patients receiving long-term opioids, oral naloxone in a daily dose equivalent to 20 to 40% of the daily opioid dose has relieved opioid-induced constipation without compromising analgesic control by competitively antagonising local opioid receptors in the gut. Doses equivalent to 10% or less of the opioid dose (in milligrams) were ineffective. However, other studies have found adverse effects even at low doses of naloxone. (2, 5-10)

**Fixed dose oral prolonged release (PR) oxycodone and prolonged release (PR) naloxone combination tablet**

Oxycodone is an opioid analgesic which has an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as an opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the central nervous system (CNS). It is given orally or by subcutaneous or intravenous injection for the relief of moderate to severe pain. 10mg of oral oxycodone is equivalent to about 20mg of oral morphine. Most patients do not require more than 400mg oxycodone daily. Constipation is considered as a very common side effect with oxycodone, occurring in ≥ 1 in 10 people who take the medicine. (2, 6)

Naloxone is present in the combination preparation at 50% of the opioid dose. However, the bioavailability of naloxone after oral administration is <3% because of first pass metabolism, therefore a clinically relevant systemic (specifically central nervous system) effect is unlikely. (6) As the effects of immediate release oral naloxone are transient, a prolonged release formulation has been developed to be combined with prolonged release oxycodone.

The PR oxycodone/PR naloxone combination was originally approved in Germany in 2006. Since the launch in Germany, over 200,000 patients have been treated with the PR oxycodone/PR naloxone combination. The formulation was approved in the UK by the Medicines & Healthcare Regulatory Agency (MHRA) in December 2008 following approval by the Mutual Recognition Process in October 2008. (11)

The licensed indication for the fixed dose PR oxycodone and PR naloxone combination tablet is 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. (6) It should be noted that the Summary of Product Characteristics (SPC) states that safety and efficacy of the product are not established in cancer patients and/or patients with liver metastasis (6). This is because patients with cancer pain were excluded from the phase III randomised clinical trials. There is data on use in cancer patients from observational studies which has not been published yet. (11)

**Dose**

The PR oxycodone and PR naloxone combination tablet is currently available in 2 strengths – 20mg oxycodone + 10mg naloxone (20mg/10mg) and 10mg oxycodone + 5mg naloxone (10mg/5mg). The PR oral tablet should be given every 12 hours. (6) The usual starting dose for an opioid naïve patient is 10mg/5mg, patients already receiving opioids may be started on higher doses, depending on their previous opioid experience. (6)
The maximum daily dose of PR oxycodone/PR naloxone is currently limited to 40mg/20mg (corresponding to twice daily administration of 20mg/10mg PR tablets). Patients requiring higher doses should be administered supplemental PR oxycodone at the same time intervals, taking into account the maximum daily dose of 400mg prolonged-release oxycodone. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be reduced. (6, 11)

Some patients taking PR oxycodone/PR naloxone according to a regular time schedule require immediate release analgesics as "rescue" medication for breakthrough pain. The PR fixed dose combination is not intended for the treatment of breakthrough pain. For the treatment of breakthrough pain, a single dose of “rescue medication” should amount to one sixth of the equivalent daily dose of oxycodone hydrochloride. The need for more than two “rescues” per day is usually a sign that the dose of the PR fixed dose combination requires upward adjustment. This adjustment should be made every 1-2 days in steps of 2 x daily 10mg/5mg PR oxycodone/PR naloxone until a stable dose is reached. The aim is to establish a patient-specific twice daily dose that will maintain adequate analgesia and make use of as little rescue medication as possible for as long as pain therapy is necessary. (6)

In non-malignant pain therapy, daily doses of up to 40mg/20mg PR oxycodone/PR naloxone are usually sufficient, but higher doses of PR oxycodone hydrochloride may be needed. (6)

The PR tablets can be taken with or without food with sufficient liquid, however they must be swallowed whole, and not broken or chewed. The tablets are a dual polymer matrix intended for oral use only. Any disruption to the dual-polymer matrix leads to a faster release of the active substances and the absorption of a possibly fatal dose of oxycodone. The empty tablet matrix may be visible in the stool. (6, 11)

The PR fixed dose combination should not be administered for longer than necessary. If long-term pain treatment is necessary given the nature and severity of the illness, careful and regular monitoring is required to establish to what extent further treatment is necessary. When the patient no longer needs opioid therapy, it is necessary to taper the dose gradually to prevent withdrawal symptoms from the oxycodone. (6)

**Special populations**

The PR fixed dose combination is not recommended for children below the age of 18 years due to a lack of data on safety and efficacy. (6)

Clinical trials have shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic and renal impairment. Naloxone concentrations were affected to a higher degree than oxycodone. The clinical relevance of a relative high naloxone exposure in hepatically impaired and renally impaired patients is not yet known. Caution must be exercised when administering PR oxycodone/PR naloxone to patients with mild hepatic impairment or renal impairment. (6)

Careful medical monitoring is particularly necessary for patients with severe renal impairment to prevent excessive sedation and coma. (11)

PR oxycodone/PR naloxone should only be used during pregnancy if the benefit outweighs the possible risks to the unborn child or neonate. Breast-feeding should be discontinued during treatment with PR oxycodone/PR naloxone. (6)
**Contraindications / precautions for use**

Contraindications listed in the Summary of Product Characteristics (SPC) are -

- Hypersensitivity to the active substances or to any of the excipients
- Any situation where opioids are contraindicated
- Severe respiratory depression with hypoxia and/or hypercapnia; severe chronic obstructive pulmonary disease
- Cor pulmonale
- Acute severe bronchial asthma
- Non-opioid induced paralytic ileus
- Moderate to severe hepatic impairment

If abused parenterally, intranasally or orally by individuals dependent on opioid agonists such as heroin, methadone or morphine, abuse of the combination product is expected to produce marked withdrawal symptoms because of the opioid receptor antagonist characteristics of naloxone or it will intensify withdrawal symptoms already present. (6)

The major risk from opioids is respiratory depression. Caution must be exercised when administering oxycodone/naloxone to elderly or infirm patients, patients with opioid-induced paralytic ileus, patients presenting severely impaired pulmonary function, myxoedema, hypothyroidism, Addison’s disease (adrenal cortical insufficiency), toxic psychosis, cholelithiasis, prostate hypertrophy, alcoholism, delirium tremens, pancreatitis, hypotension, hypertension, pre-existing cardiovascular diseases, head injury (due to the risk of increased intracranial pressure), epileptic disorder or predisposition to convulsions, or patients taking monoamine oxidase (MAO) inhibitors. (6)

During long-term administration, the patient may develop tolerance to the drug and require higher doses to maintain the desired analgesic effect. Chronic administration of PR oxycodone/ with or without PR naloxone may lead to physical dependence. Withdrawal symptoms may occur upon the abrupt cessation of therapy. If therapy with oxycodone/naloxone is no longer required, it may be advisable to reduce the daily dose gradually. (6)

PR oxycodone/PR naloxone may impair the ability to drive and use machines. This is particularly likely at the beginning of treatment, after dose increase or product rotation and if the product is combined with alcohol or other CNS depressant agents. Patients stabilised on a specific dosage will not necessarily be restricted. Therefore, patients should consult with their physician as to whether driving or the use of machinery is permitted. (6)

**Interactions**

No interaction studies have been performed. (6)

Substances having a CNS-depressant effect (e.g. alcohol, other opioids, sedatives, hypnotics, anti-depressants, sleeping aids, phenothiazines, neuroleptics, anti-histamines and anti-emetics) may enhance the CNS-depressant effect (e.g. respiratory depression and sedation) of the oxycodone/naloxone combination. (6)

Clinically relevant changes in coagulation, as measured by the International Normalised Ratio (INR) in both directions have been observed in individuals if oxycodone and coumarin anticoagulants (e.g. warfarin) are taken together. (6)

In vitro metabolism studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, the oxycodone/naloxone combination is not expected to cause clinically relevant interactions with other concomitantly administered drugs metabolised over...
the cytochrome P (CYP) isomers CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4. In addition, the likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal. (6)

**Side effects**

In the Summary of Product Characteristics (SPC), side effects have been classified as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) and not known (can not be estimated from the available data. (6)

There are no very common or very rare side effects reported for the PR oxycodone/PR naloxone tablets.

Common side effects of the combination tablet are - decreased appetite up to loss of appetite, anxiety, restlessness, headache, sedation, tremor, vertigo, decrease in blood pressure, rhinorrhea, yawning, abdominal pain, diarrhoea, dry mouth, flatulence, vomiting, nausea, pruritis, skin reactions, hyperhidrosis, muscle spasms, muscle twitching, myalgia, drug withdrawal syndrome, feeling hot and cold, chills, asthenia. (6)

There are also a number of uncommon side effects listed. (6)

**Clinical Evidence**

There are a number of trials that have reviewed the pharmacokinetics, clinical pharmacology, clinical efficacy and patient acceptability of the fixed dose, PR, combination product.

Four clinical studies have demonstrated clinical efficacy in terms of pain relief and bowel function – 1 phase II study (12, 13) and 3 phase III studies (14-16), these are discussed below.

**Phase II data**

Meissner et al randomised 202 adult patients aged 18 years or over who were experiencing severe chronic pain, of mainly non-cancer origin, that required opioid treatment or were currently stable on PR oxycodone (40, 60 or 80mg/day). (12) The study evaluated the analgesic efficacy of PR oral oxycodone when given with PR oral naloxone and assessed its impact on opioid induced constipation. The study also aimed to identify the optimal dose ratio of oxycodone and naloxone.

The study was a multicentre, prospective, placebo controlled, randomised, double blind, parallel group trial conducted in 28 centres in Germany. Exclusion criteria included current alcohol or drug abuse, current acute pancreatitis, current severe cardiovascular or respiratory diseases (e.g. lung cancer or metastases), current severe renal or liver impairment (transaminase levels 3 times above normal range), liver or renal carcinoma or metastases.

The study had 3 phases – pre-randomisation (patient screening and titration/run-in), maintenance (a double blind treatment period) and an open label phase.

Following screening, patients with inadequate pain control or those who were taking an opioid other than oxycodone, entered a 2 week titration period and were individually titrated and stabilised to oxycodone PR 40, 60 or 80mg/day. Patients already stable on oxycodone with concomitant constipation entered a 7 day run in period before the maintenance phase.

At the end of the 2 week titration or 7 day run in period, patients were eligible to enter the double blind maintenance phase if they had been on a stable daily dose of oxycodone (40-80mg) for 7 consecutive days, received no more than 5 rescue medications per week (defined as 1 x 10mg PR oxycodone tablet) and required laxatives to have at
least 3 bowel evacuations per week.

For the maintenance phase, patients were randomised to 4 groups depending on the dose of naloxone – 10, 20 or 40mg or placebo. For each patient the total study duration was up to 10 weeks, including the screening period, titration or run-in phase, 4 week treatment period and an open label phase of 2 weeks when patients stopped taking naloxone but continued with oxycodone.

The primary efficacy outcomes were mean pain intensity and mean bowel function. Pain was assessed subjectively using a numerical analogue scale (NAS) where 0 = no pain and 100 = worst imaginable pain. The NAS was completed twice daily, 2 hours after medication administration. Mean pain intensity was calculated at the end of the titration/run in phase, maintenance phase and open label phase. Bowel function was also assessed on a NAS at similar time points with the bowel function index (BFI). Higher scores with the BFI indicate poor bowel function.

The BFI was the mean of the following items, which patients assessed at each visit (patients were asked to consider the last seven days when giving their assessments; for each of the measures, a lower score indicates better bowel function):
- Ease of defaecation (assessed using a numerical analogue scale, where 0 = easy/no difficulty and 100 = severe difficulty).
- Feeling of incomplete bowel evacuation (assessed using a numerical analogue scale, where 0 = not at all and 100 = very strong).
- Personal judgment of constipation (assessed using a numerical analogue scale, where 0 = not at all and 100 = very strong).

Higher scores with the BFI indicate poor bowel function. A change in BFI score of >12 points is considered to be clinically relevant. (17)

166 patients completed the study, although the intent to treat (ITT) population was 196 as this included all randomised patients who received at least 1 dose of PR naloxone or placebo and had at least 1 efficacy assessment. All treatment groups were well balanced with respect to demographic and baseline characteristics. Back pain was the most common reason for pain (24.3%) followed by post-operative complications (15.3%). Only 2.5% of patients had tumour related pain.

There were no significant differences in the intensity of mean pain between the treatment groups at any of the study time points. The results also indicated that the addition of PR naloxone did not reduce the analgesic efficacy of PR oxycodone.

As the PR naloxone dose increased, the BFI scores decreased. At the end of the maintenance phase the differences between the 20mg and 40mg doses of PR

Table 1 – PR oxycodone & PR naloxone dose groups

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
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</thead>
<tbody>
<tr>
<td>PR oxycodone / PR naloxone dose ratio</td>
<td>40/placebo</td>
<td>60/placebo</td>
<td>80/placebo</td>
<td>40/40, 1:1</td>
</tr>
<tr>
<td></td>
<td>40/10, 4:1</td>
<td>60/10, 6:1</td>
<td>80/10, 8:1</td>
<td>40/20, 2:1</td>
</tr>
<tr>
<td></td>
<td>60/10, 6:1</td>
<td>80/10, 8:1</td>
<td>80/20, 4:1</td>
<td>60/40, 1.5:1</td>
</tr>
<tr>
<td></td>
<td>80/10, 8:1</td>
<td>80/20, 4:1</td>
<td>80/40, 2:1</td>
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</table>
naloxone and placebo were statistically significant (p<0.05). Bowel function scores at the end of the maintenance phase were lowest in the 1:1, 1.5:1 and 2:1 dose ratios. The removal of PR naloxone from the treatment regimen resulted in an increase in BFI scores. The study showed that bowel function improves progressively as the PR oxycodone/PR naloxone ratio decreases i.e. the improvement with the 2:1 dose ratio was approximately 50% higher than the 4:1 dose ratio and there was minimal improvement from the 2:1 ratio to the 1.5:1 ratio.

The incidence of adverse events during the maintenance phase was comparable across all treatment groups, although the number of events increased with the increasing PR naloxone dose. Most adverse effects were mild to moderate in intensity. The incidence of diarrhoea was higher among patients taking PR naloxone and increased with higher doses. The incidence of serious adverse events was low and generally comparable across all active PR naloxone groups. The frequency of discontinuations due to adverse events in the maintenance phase increased with increasing doses of PR naloxone. The main reason for discontinuation was diarrhoea. The mean (± standard deviation, SD) number of days with laxative intake during the last 7 days of the maintenance phase decreased with increasing absolute dose of naloxone. The number of patients taking laxatives during the last 7 days of the maintenance phase also decreased with increasing absolute dose of naloxone. Results are detailed in table 2.

The study demonstrated non-inferiority of the PR oxycodone/PR naloxone combination versus PR oxycodone alone for analgesic efficacy and superiority of the PR oxycodone/PR naloxone combination versus PR oxycodone for effect on the bowel. Based on the safety and efficacy results, the optimal PR oxycodone/PR naloxone ratio was 2:1.

A paper assessing the patients’ and investigators’ views on the efficacy and tolerability of the PR oxycodone/PR naloxone combination used in the Meissner et al study has been published. (13)

Assessment of efficacy and tolerability was completed at the end of the maintenance phase using a 7 point rating scale ranging from very good to very poor. Patients and investigators provided their ratings independently. Preference for the maintenance phase (PR oxycodone/PR naloxone) or the titration/run in phase (oxycodone alone) regarding tolerability and efficacy was also assessed at the end of the maintenance phase.

Overall treatment efficacy improved with increasing PR naloxone dose and

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Table 2 – Incidence of discontinuations & laxative use in Meissner et al study

<table>
<thead>
<tr>
<th>PR naloxone daily dose</th>
<th>Placebo</th>
<th>10mg</th>
<th>20mg</th>
<th>40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of diarrhoea</td>
<td>12%</td>
<td>19.6%</td>
<td>23.5%</td>
<td>36%</td>
</tr>
<tr>
<td>Discontinuations due to adverse events in the maintenance phase</td>
<td>2%</td>
<td>9.8%</td>
<td>11.8%</td>
<td>18%</td>
</tr>
<tr>
<td>Discontinuation due to diarrhoea</td>
<td>0%</td>
<td>2%</td>
<td>7.8%</td>
<td>12%</td>
</tr>
<tr>
<td>Mean (± SD) no. of days with laxative intake during the last 7 days of the maintenance phase</td>
<td>3.9 (±3.38)</td>
<td>2.6 (±3.34)</td>
<td>2.0 (±3.14)</td>
<td>1.6 (±2.93)</td>
</tr>
<tr>
<td>No. of patients taking laxatives during the last 7 days of the maintenance phase</td>
<td>35 (81%)</td>
<td>26 (70%)</td>
<td>18 (45%)</td>
<td>21 (58%)</td>
</tr>
</tbody>
</table>
was rated by most patients as ‘good’ or ‘very good’. Tolerability of the increasing naloxone doses did not differ greatly. The responses of the investigators to the same parameters were similar to those of the patients. More patients preferred the maintenance phase and there was a similar pattern of results with respect to efficacy and tolerability. The 2:1 dose ratio was rated highly by patients taking active naloxone for efficacy and tolerability. Results are set out in table 3.

The authors of the paper concluded that in terms of patient assessment, a combination of PR oxycodone and naloxone is effective and well tolerated for treatment of severe chronic pain.

**Phase III data**

*Vondrackova et al* conducted a phase III trial to assess analgesic efficacy and safety of oxycodone in combination with naloxone in a PR tablet formulation. (11, 14)

The study enrolled adults over 18 years old if they had a history of moderate to severe chronic non-malignant lower back pain which was currently managed by an opioid analgesic. Exclusion criteria included hypersensitivity to oxycodone, naloxone or related products, patients currently receiving the equivalent of <10mg or >40mg/day oxycodone, patients diagnosed with cancer, active alcohol or drug abuse, abnormal liver function tests and a history of >2 lower back operations.

The primary objective of the study was to demonstrate the analgesic superiority of PR oxycodone and PR naloxone over placebo measured as the time from the initial dose of study medication to recurrent pain events (defined as inadequate analgesia) during the double blind phase. There were also a number of secondary and exploratory objectives. Secondary objectives included average daily pain during treatment, sleep quality with PR oxycodone/PR naloxone compared to placebo and PR oxycodone and the total amount of rescue medication used. Exploratory objectives included an assessment of pain interference on daily activities and the effect on constipation during treatment with PR oxycodone/PR naloxone compared to placebo and PR oxycodone.

<table>
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<tr>
<td><strong>PR Naloxone daily dose</strong></td>
<td>Placebo</td>
<td>10mg</td>
<td>20mg</td>
</tr>
<tr>
<td><strong>Overall treatment efficacy: good or very good</strong></td>
<td>43.5%</td>
<td>50%</td>
<td>67.4%</td>
</tr>
<tr>
<td><strong>Overall treatment tolerability: good or very good</strong></td>
<td>71.7%</td>
<td>83.3%</td>
<td>79.1%</td>
</tr>
<tr>
<td><strong>Preference for the maintenance phase for efficacy</strong></td>
<td>34.8%</td>
<td>45.2%</td>
<td>44.2%</td>
</tr>
<tr>
<td><strong>Preference for the maintenance phase for tolerability</strong></td>
<td>34.8%</td>
<td>54.8%</td>
<td>60.5%</td>
</tr>
<tr>
<td><strong>2:1 dose ratio efficacy: good or very good</strong></td>
<td>43.5%</td>
<td>70.4%</td>
<td></td>
</tr>
<tr>
<td><strong>2:1 dose ratio tolerability: good or very good</strong></td>
<td>71.5%</td>
<td>81.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Number of adverse events</strong></td>
<td>111</td>
<td>119</td>
<td>129</td>
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randomisation phase, a double-blind phase and an extension phase. During the 4 week pre-randomisation phase patients were screened and underwent opioid tapering and titration to confirm the need for opioid medication and to achieve an adequate dose of oxycodone for analgesia. At the start of the 12 week double blind phase patients were randomised in a 1:1:1 ratio to twice daily PR oxycodone/PR naloxone (10/5mg or 20/10mg), PR oxycodone (10mg or 20mg) or placebo. All patients were allowed to use immediate release oxycodone every 4-6 hours as required as rescue medication at a quarter of the dose of the total daily opioid intake. For patients who completed the double blind phase, there was an option to enter a 12 month extension study to assess the long term safety and efficacy of PR oxycodone/PR naloxone.

751 patients were enrolled in the study; after screening failures (n=75), discontinuations during the opioid tapering (n=73) and run-in phases (n=139), 464 patients were randomised to study medication. 1 patient did not receive any study medication; therefore the full analysis population comprised 463 patients. All treatment groups were well balanced with respect to demographic and baseline characteristics. A high percentage of patients (80.3%) had a low BFI value at baseline indicating only mild or no constipation.

The results for the study are detailed in table 4. The primary objective of the study was to demonstrate the analgesic superiority of PR oxycodone/PR naloxone over placebo measured as the time from the initial dose of study medication to recurrent pain events (defined as inadequate analgesia) during the double blind phase. Pain events in the PR oxycodone/PR naloxone group occurred 12-15 days later than in the placebo group. Times to recurrent pain events were significantly shorter in the placebo group than the PR oxycodone/PR naloxone group. No statistically significant differences were detected between the PR oxycodone/PR naloxone and PR oxycodone groups. The risk of experiencing a pain event was 42% lower with PR oxycodone/PR naloxone compared to placebo (p<0.0001). The risk of experiencing a pain event was 6% higher with PR oxycodone/PR naloxone compared to PR oxycodone, but this was not statistically significant.

The secondary objectives showed a similar pattern to the primary objective. The PR oxycodone and PR oxycodone/PR naloxone groups had statistically significantly lower average pain scores over the last 24 hours compared to placebo, a significant improvement in sleep interference and a lower requirement for rescue medication.

In a subgroup of patients who were moderately or severely constipated, a clinically relevant difference in BFI score was observed between the PR oxycodone and PR oxycodone/PR naloxone groups between visits 4 and 8. No statistical analysis was done as there were an insufficient number of patients. The percentage of patients who had an increase of at least 1 or at least 3 complete spontaneous bowel movements (CSBMs) before the end of the double blind phase compared with the week before baseline was higher in the PR oxycodone/PR naloxone group compared to the PR oxycodone group. Laxative use was also assessed in the subgroup of patients who were moderately or severely constipated. Laxative intake (mean percentage of days with laxative use) decreased over the course of the double blind phase in the PR oxycodone/PR naloxone group and increased in the PR oxycodone group.

The incidence of adverse effects during the double blind phase was comparable between the different treatment groups.
Constipation (8.4%), nausea (7.1%), headache (4.8%), vomiting (4.3%) and diarrhoea (4.1%) were the most frequently reported treatment emergent adverse events. Most adverse events were mild or moderate in intensity and the incidence of severe adverse events was low. The incidence of adverse events leading to discontinuation during the double blind phase was very low as was the number of serious adverse events.

The results show that pain events are less likely to occur with PR oxycodone/PR naloxone compared to placebo, as would be expected, and PR oxycodone/PR naloxone is comparable to PR oxycodone with regard to incidence of pain events. The addition of PR naloxone to PR oxycodone does not negatively affect the analgesic efficacy of PR oxycodone. There is a clinically relevant improvement in bowel function with PR oxycodone/PR naloxone compared to PR oxycodone alone.

**Simpson et al** conducted a randomised, double-blind, double dummy, parallel-group, multicentre, 12 week, phase III study to evaluate the impact of PR oxycodone/PR naloxone compared to PR oxycodone alone on symptoms of constipation secondary to opioid treatment of moderate to severe noncancer pain. (11, 15)

The study enrolled adults over 18 years old who were taking continuous opioid therapy (oxycodone equivalent of ≥ 20mg/day and ≤ 50mg/day) for moderate to severe non-cancer pain and who were suffering from constipation caused or aggravated by an opioid. Exclusion criteria included history of hypersensitivity to oxycodone or naloxone:

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**Table 4 – Efficacy and safety results from the Vondrackova et al study**

<table>
<thead>
<tr>
<th></th>
<th>PR Oxycodone/ naloxone</th>
<th>PR Oxycodone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomised</td>
<td>154</td>
<td>151</td>
<td>158</td>
</tr>
<tr>
<td>Mean time to first pain event</td>
<td>32.2 days</td>
<td>33.7 days</td>
<td>19.3 days</td>
</tr>
<tr>
<td>Statistical difference in average pain score over last 24 hrs</td>
<td>P=0.0396 vs. placebo</td>
<td>P=0.0080 vs. placebo</td>
<td>-</td>
</tr>
<tr>
<td>Statistical difference in sleep interference scores</td>
<td>P=0.0057 vs. placebo</td>
<td>P=0.0030 vs. placebo</td>
<td>-</td>
</tr>
<tr>
<td>Statistical difference in rescue medication intake</td>
<td>P=0.0004 vs. placebo</td>
<td>P&lt;0.0001 vs. placebo</td>
<td>-</td>
</tr>
<tr>
<td>Number of patients moderately or severely constipated</td>
<td>29</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Reduction in BFI scores between visit 4 and 8</td>
<td>23.1</td>
<td>11.3</td>
<td>-</td>
</tr>
<tr>
<td>Mean change in the number of CSBMs</td>
<td>Increase of 2.27/week (1.93 to 4.20)</td>
<td>Decrease of 0.32/week (2.40 to 2.08)</td>
<td>-</td>
</tr>
<tr>
<td>Increase of at least 1 CSBM</td>
<td>62.1%</td>
<td>23.3%</td>
<td>-</td>
</tr>
<tr>
<td>Increase of at least 3 CSBMs</td>
<td>62.1%</td>
<td>33.3%</td>
<td>-</td>
</tr>
<tr>
<td>Change in the mean % of days with laxative intake</td>
<td>Decrease from 18.4% to 15.6%</td>
<td>Increase from 13.7% to 24.3%</td>
<td>-</td>
</tr>
<tr>
<td>Incidence of adverse events for total study population</td>
<td>55.8%</td>
<td>53%</td>
<td>52.5%</td>
</tr>
</tbody>
</table>
patients with cancer pain, rheumatoid arthritis, evidence of clinically unstable disease or evidence of impaired liver/kidney function; significant structural abnormalities of the GI tract or any diseases or conditions that affect bowel transit; pregnant or breast feeding women.

As in previous studies there was a pre-randomisation (screening and run-in) phase, a double blind phase and an extension phase. During the run in period, which lasted from 7-28 days, patients who were not taking oxycodone were converted to oxycodone PR and the dose was titrated to optimum analgesic effect. Patients taking laxatives before the study were converted to oral bisacodyl 10mg/day unless they were already taking this. Patients were allowed to continue with daily fibre supplements or bulking agents, provided that they remained on a stable dose and could maintain adequate hydration.

At the start of the 12 week double blind phase, patients were randomised to PR oxycodone/PR naloxone (2:1 fixed dose ratio) or PR oxycodone. All patients who completed the double blind phase were eligible to enter an optional 52 week extension phase in which all patients received PR oxycodone/PR naloxone.

Efficacy data were collected in daily diaries and during 8 study visits. The primary objective was to assess whether PR oxycodone/PR naloxone lead to improvements in constipation, as measured by the BFI, compared to patients taking PR oxycodone alone after 4 weeks of treatment. The period of 4 weeks was chosen because the phase II study suggested that this was the optimum period for detection of alteration of bowel habit. The BFI score was defined as the mean score of 3 distinct bowel dysfunction components on the scale: ease of defecation (0 = easy / no difficulty, 100 = severe difficulty); feeling of incomplete bowel evacuation (0 = not at all, 100 = very strong) and judgement of constipation (0 = not at all, 100 = very strong). Higher scores indicate poor bowel function. Secondary objectives were assessment of the improvements in symptoms of constipation and average pain over the last 24 hours which was assessed at each study visit. Exploratory objectives included the mean number of CSBMs per week, severity and interference of pain and the frequency of laxative and rescue medication use. Rescue medication was immediate release oxycodone 5mg which could be taken every 4 hours as required. Adverse events were also monitored.

322 patients were randomised to treatment and there were no differences between the 2 groups at baseline with regards to demographics, BFI or pain intensity. Osteoarthritic pain and neuropathic pain were the most common reasons for use of the opioid. A significant improvement was seen after the first week of treatment and after 4 weeks, the mean BFI score in the PR oxycodone/PR naloxone group had dropped 26.9 points compared to 9.4 points in the PR oxycodone group. Results are presented in table 5. Throughout the first 4 weeks of the double blind phase the difference between the mean BFI scores was statistically significant and in favour of the PR oxycodone/PR naloxone group (-15.2, p<0.0001; 95% CI -18.2 to -12.2). The BFI score continued to reduce to the end of the study and the difference between the 2 groups remained statistically significant to the end of the study.

A similar pattern was also observed for the secondary and exploratory outcomes. After 4 weeks, the difference between the 2 groups for symptoms of constipation was statistically significant in favour of the PR oxycodone/PR naloxone group (-3.54, p<0.0001; 95% CI -4.56 to -2.51).
After 4 weeks, the difference in number of CSBMs was statistically significant in favour of the PR oxycodone/PR naloxone group (-1.66, p<0.0001; 95% CI 1.33 to 2.07) as was the number of patients who required laxatives (p<0.0001).

Pain intensity and average pain remained stable throughout the double blind phase and was comparable between the treatment groups.

Overall the incidence of adverse events was similar between the 2 groups. The most common class of adverse events was gastrointestinal (GI), although there were fewer events in the PR oxycodone/PR naloxone group. In particular, the incidence of nausea, vomiting, abdominal pain and dyspepsia was lower. Serious adverse events included GI haemorrhage, headache and cerebrovascular accident. Fewer patients discontinued treatment due to adverse effects with PR oxycodone/PR naloxone.

The authors conclude that study shows that a fixed dose PR oxycodone/PR naloxone combination is effective in reducing the impact of opioid induced constipation as seen by the reduction in BFI and increase in number of CSBMs per week. The combination product is superior to PR oxycodone monotherapy with respect to change in bowel function while still having the same analgesic efficacy.

The manufacturers have data on file about another randomised, double blind, double dummy, parallel group, multicentre trial comparing PR oxycodone/PR naloxone to PR oxycodone in patients with non-malignant pain with a similar design to the Simpson et al study. The main difference was that the was 60-80mg/day (11, 16).

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Table 5 - Efficacy and safety results from the Simpson et al study

<table>
<thead>
<tr>
<th></th>
<th>PR Oxycodone/ naloxone</th>
<th>PR Oxycodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients randomised</td>
<td>162</td>
<td>160</td>
</tr>
<tr>
<td>Full analysis population for efficacy results</td>
<td>158</td>
<td>158</td>
</tr>
<tr>
<td>Baseline mean BFI score (SD)</td>
<td>61.8 (22.95)</td>
<td>61.0 (23.39)</td>
</tr>
<tr>
<td>Mean BFI score after 4 weeks (SD)</td>
<td>34.9 (25.80)</td>
<td>51.6 (26.78)</td>
</tr>
<tr>
<td>Mean score for symptoms of constipation after 4 weeks (SD)</td>
<td>6.4 (5.29)</td>
<td>9.4 (6.83)</td>
</tr>
<tr>
<td>Mean number of CSBMs at baseline (SD)</td>
<td>1.1 (1.64)</td>
<td>1.1 (1.64)</td>
</tr>
<tr>
<td>Mean number of CSBMs after 4 weeks (SD)</td>
<td>3.5 (2.81)</td>
<td>2.4 (2.56)</td>
</tr>
<tr>
<td>Number of patients who achieved ≥ 3 CSBMs/week after 4 weeks</td>
<td>94</td>
<td>54</td>
</tr>
<tr>
<td>Number of patients who took laxatives during the 4 week period</td>
<td>49</td>
<td>87</td>
</tr>
<tr>
<td>Number of patients experiencing gastrointestinal adverse events</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Number of patients experiencing serious adverse events</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients discontinuing due to adverse events</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>
278 patients were randomised in a 1:1 ratio to a 12 week double blind phase and 265 patients received study medication (n=135 for PR oxycodone, n=130 for PR oxycodone/PR naloxone). The results of this trial followed the same pattern as the Simpson et al study. After 4 weeks the BFI score for the PR oxycodone/PR naloxone dropped by 26.46 points compared to 10.84 points for PR oxycodone. This reduction was considered clinically relevant. A statistically significant improvement in bowel function was seen with PR oxycodone/PR naloxone after the first week of the double blind phase and continued until the end of the study. There was no statistically significant difference in pain intensity between the 2 groups indicating that PR naloxone does not affect the analgesic efficacy of PR oxycodone. Patients using PR oxycodone/PR naloxone showed improvement in symptoms of constipation that was also considered to be clinically relevant. 86 patients in the PR oxycodone group used laxatives compared with 56 people in the prolonged release PR oxycodone/PR naloxone group. Most adverse effects were of mild to moderate severity. The number of patients with adverse events and serious adverse events was slightly higher in the PR oxycodone/PR naloxone group compared to the PR oxycodone group.

**Long term data**

The extension phase data from the Vondrackova et al and Simpson et al trials is not included in the published reports of the trials and is not yet available. (11, 14, 15)

The manufacturers have long term data on file for 12 month open label extensions to the Vondrackova et al and Simpson et al studies. (18, 19)

Patients who completed the double blind phase, required continuation of daily treatment with opioids and were likely to benefit from chronic opioid therapy were eligible to enter the open label extension. (18) Patients were started on PR oxycodone/PR naloxone 20/10mg per day. The dose could be increased to 80/40mg per day if required using 40/20mg tablets which are not currently available in the UK. The primary objective was to assess long term efficacy and safety – there was no primary efficacy measure.

380 patients entered the study and 379 received open label medication, 296 completed the study. The most common reason for discontinuation was patient choice. Patient scores for average pain over the last 24 hours, pain intensity, and interference of pain with sleep and activities remained low and stable throughout the 12 month period. The mean exposure to PR oxycodone/PR naloxone was 320.5 days. During the extension study the mean daily dose of PR oxycodone/PR naloxone increased which possibly indicates a natural progression of the underlying chronic pain condition or increasing drug tolerance. Use of rescue medication was low. Approximately 10% of patients required regular additional laxatives. (19) The studies demonstrate that PR oxycodone/PR naloxone is effective if used for up to 12 months for treating chronic non-malignant pain.
Economic considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost per 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR oxycodone / PR naloxone</td>
<td>10mg/5mg BD or 20mg/10mg BD</td>
<td>£35.11 or £70.22</td>
</tr>
<tr>
<td>PR oxycodone</td>
<td>10mg BD or 20mg BD</td>
<td>£26.45 - £52.89</td>
</tr>
<tr>
<td>PR morphine</td>
<td>30mg BD</td>
<td>£9.77 - £13.17 depending on preparation used</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>10mg/day</td>
<td>£1.83</td>
</tr>
<tr>
<td>Senna</td>
<td>15-30mg ON</td>
<td>£0.83 - £1.65</td>
</tr>
<tr>
<td>Ispaghula husk</td>
<td>1 sachet (3.5g) in water, 1-3 times daily</td>
<td>£2.07 - £10.75 depending on preparation used</td>
</tr>
<tr>
<td>Lactulose</td>
<td>15ml BD</td>
<td>£4.87</td>
</tr>
<tr>
<td>Macrogol</td>
<td>1-3 sachet/day</td>
<td>£6.49 - £19.47</td>
</tr>
</tbody>
</table>

NHS prices, January 2009. Doses are shown for general comparison and do not imply therapeutic equivalence.

Conclusions from the clinical evidence

- Based on safety and efficacy data from phase II trials, the optimal PR oxycodone/PR naloxone ratio is 2:1.
- In line with the licensed indication, the combination product is recommended for the treatment of severe non-malignant pain.
- Safety and efficacy of the product are not established in cancer patients and/or patients with liver metastasis as demonstrated by the clinical trials which have been completed with the PR oxycodone/PR naloxone combination.
- The analgesic efficacy of the PR oxycodone/PR naloxone combination is equivalent to PR oxycodone formulations.
- Use of PR oxycodone/PR naloxone leads to a clinically relevant improvement in bowel function compared to PR oxycodone monotherapy, although laxatives are still required on a regular basis by about 10% of patients in long term studies.
- The trials showed that the addition of PR naloxone does not affect the analgesic efficacy of PR oxycodone.
- The incidence of adverse effects is comparable between the different treatment groups.
- PR oxycodone/PR naloxone has not yet been compared to other opioids or opioid + concomitant laxatives.
- To date there is no clinical experience to refer to for switching from other analgesics to the PR oxycodone/PR naloxone fixed dose combination.

Place in therapy

- The Scottish Medicines Consortium (SMC) reviewed PR oxycodone/PR naloxone in March 2009. The advice issued was that 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 economic analysis presented was not sufficiently robust to gain acceptance by the SMC. (20)
- PR oxycodone can be used in patients who require an opioid but cannot tolerate morphine. (5) PR oxycodone/PR naloxone could therefore be used in patients who can not tolerate morphine due to opioid induced constipation.
- PR oxycodone/PR naloxone may be an option for patients who require a strong opioid and have experienced constipation while taking weak opioids (e.g. tramadol, codeine). (11)
- Use of a PR oxycodone/PR naloxone fixed dose combination tablet may help to reduce polypharmacy in patients taking a large number of oral medications.
References


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10. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. American Journal of Health-System Pharmacy 2003; 60: 1264-7

11. Personal communication, Napp Pharmaceuticals


20. Oxycodone/naloxone 10mg/5mg and 20mg/10mg prolonged releases tablets (Targinact). Scottish Medicines Consortium No. 541/09, March 2009


The London New Drugs Group would like to thank Dr Anthony Ordman, Consultant in Pain Medicine, Royal Free Hospital for his comments and assistance in preparing this document.

This document reflects the views of the LNDG and may not reflect those of reviewers.

The manufacturers (Napp) have been given the opportunity to comment on this review.