EXPERT OPINION





# Combined oral prolonged-release oxycodone and naloxone in chronic pain management

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***Introduction:*** The use of opioids is associated with unwanted adverse effects, particularly opioid-induced constipation (OIC). The adverse effects of opioids on gastrointestinal function are mediated by the interaction with opioid receptors in the gastrointestinal tract. The most common drugs used for relieving OIC are laxatives, which do not address the opioid receptor-mediated bowel dysfunction and do not provide sufficient relief.
***Areas covered:*** This paper discusses the role of a combination of prolonged-release formulation of oxycodone (OX) and naloxone (N) in the prevention and management of OIC, reporting efficacy and safety outcome of controlled studies. In a therapeutic area of great unmet need, the combination tablet of prolonged release of OX and N (PR OXN) could offer patients effective analgesia, while improving opioid-induced bowel dysfunction.
***Expert opinion:*** PR OXN offers a unique and specific mechanism to control OIC in patients receiving chronic opioid therapy. This combination has the potential advantage of preventing OIC, particularly in subgroups of population, like elderly or advanced cancer patients. This approach can decrease the use of laxatives and additional medications, which represent a burden for patients presenting comorbidities requiring multiple medications.

**Keywords:** cancer pain, chronic pain, opioid-antagonist, opioids, oxycodone–naloxone combination

*Expert Opin. Investig. Drugs [Early Online]*

## 1. Introduction

Approximately 20% of European population suffers from chronic pain. The most frequent causes are osteoarthritis and back pain [1]. While opioids are recognized as the mainstay of pain management for patients with cancer pain, they are also being increasingly used for the treatment of chronic non-cancer pain. However, the use of opioids is associated with unwanted adverse effects, particularly opioid-induced constipation (OIC). The adverse effects of opioids on gastrointestinal function are mediated by the interaction with opioid receptors in the gastrointestinal tract. Endogenous opioids function to coordinate the contractile process under normal conditions and suppress intestinal motility. Studies in animals and humans suggest that endogenous opioids inhibit enteric nerve activity and both propulsive motor and secretory activities [2]. The enteric mu-opioid receptors appear to be the principal mediator of opioid agonist effects on the gastrointestinal tract. When an exogen mu-opioid agonist binds to these receptors, the release of various neurotransmitters is inhibited, interrupting the coordinate rhythmic contractions required for intestinal motility and reduces mucosal secretions [3]. Different from many opioid-related adverse effects which occur at the beginning of treatment and which tend to disappear over time, constipation constantly persists and may represent a relevant problem during the chronic treatment with opioids [4]. The physical consequences of constipation demand consideration. The majority

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**Box 1. Drug summary.**

| | |
|---|---|
| Drug name | PR OXN |
| Phase | III |
| Indication | Prevention of OIC |
| Pharmacology description | Association of an opioid analgesic drug, such as OX, and an opioid antagonist, such as N, with negligible systemic reabsorption |
| Route of administration | Oral |
| Chemical structure | (5R,9R,13S,14S)-4,5α-epossi-14-idrossi-3-metossi-17-metilmorfinan-6-one ($C_{18}H_{21}NO_4$) Cloridrato di N-allil-4,5a-epossi-3, 14-diidrossi-morfinan-6-one ($C_{19}H_{21}NO_4$) |
| Pivotal trial | [6] |

of patients report some degree of negative impact on quality of life and are more likely to use healthcare resources, miss work reporting impaired ability to undertake daily activities. It is particularly challenging to obtain accurate estimates of the prevalence of constipation because of numerous other factors that may also induce constipation, particularly in cancer patients [3].

The most common drugs used for relieving OIC are laxatives, which act with different mechanisms on the bowel transit. However, laxatives do not address the mechanisms of bowel dysfunction mediated by opioid receptors and do not provide sufficient relief.

In the last decade, there had been an attempt to target the underlying mechanisms of opioid action in the gastrointestinal tract by antagonizing opioid receptors. The rationale was based on the local activity on intestinal opioid receptor and the negligible oral bioavailability of naloxone (N), which undergo extensive elimination by hepatic first-pass metabolism. The limited systemic availability of N avoids blocking the desired central analgesic effects of opioids. A number of pioneer studies have assessed the ability of oral immediate release N, also showing some evidence for slightly reduced analgesic efficacy, and intestinal withdrawal symptoms [5].

A prolonged-release formulation could confer additional benefits ensuring continual antagonism and by reducing the risk of overburdening the hepatic enzymatic system responsible for its first-pass metabolism, thus reducing the risk of N being systematically available with consequent loss of analgesic efficacy. In a therapeutic area of great unmet need, therefore, the combination tablet of prolonged release of oxycodone (OX) and N (PR OXN) could offer patients effective analgesia while improving opioid-induced bowel dysfunction (see **Box 1**).

## 2. Overview of the market

Opioids invariably cause constipation. Although other common unwanted effects, such as sedation, nausea and vomiting, tend to improve with continued use and often resolve completely, OIC does not get better with repeated administration. Laxatives are commonly used, but their effects do not specifically affect the cause of constipation. By contrast, drugs with a specific mechanism, such as antagonism with intestinal opioid receptors, may provide a therapeutic effect with a reduce impact of OIC. Targeted therapies, with a combination of opioids with an opioid antagonist focusing on the specific mechanism of OIC may reduce gastrointestinal adverse effects, while maintaining systemic analgesia. The aim of therapy with PR OXN is to offer analgesic therapy with an opioid compound like OX while providing a prevention of constipation, which is one of the most frequent opioid-related adverse effect, through the association with N. PR OXN represents a recent and widely used therapy, approved for the treatment of severe pain which can be adequately managed only with opioids.

## 3. Introduction to the compound

PR OXN in a single formulation tablet has been designed with the intent to prevent or reduce OIC. The coadministration of OX and N optimal ratio in a fixed ratio of 2:1 did not significantly alter the bioavailability of either of its constituents [6]. A scintigraphic analysis showed that 20 mg of OX significantly increased colon arrival time and PR OXN 20/10 mg significantly reduced mean colonic transit time at values similar to placebo [7]. Two studies provided information about the optimal ratio of OX and N to obtain a significant improvement in bowel transit without influencing analgesia. To identify the optimal dose ratio of OX and N, 202 patients with chronic pain receiving stable doses of PR OX in the range of 40 – 80 mg/day, were randomized to receive 10, 20 and 40 mg/day of N or placebo. After a 4-week maintenance phase, patients received OX only for 2 weeks. No loss of analgesic efficacy with N was observed. Mean pain intensity scores on randomization were comparable to placebo, 10, 20 and 40 mg N dose, and remained unchanged during treatment. Bowel function improved with increasing N dose. N in doses of 20 and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo. There was a trend toward an increased incidence of diarrhea with higher doses of N. The 2:1 OX:N ratio was identified as the most suitable for further development [8]. Similarly, to evaluate the optimal dose ratio for PR OXN, patients with cancer and non-cancer pain requiring opioid therapy in the range of 40 – 80 mg of OX, were randomized to receive 10, 20 and 40 mg of N, or placebo every 12 h for 4 weeks. The better ratio for efficacy and tolerability, as estimated by patients, was 2:1 [9].

## 4. Chemistry

The molecular formula of OX and N, in comparison with morphine is reported in **Figure 1**.

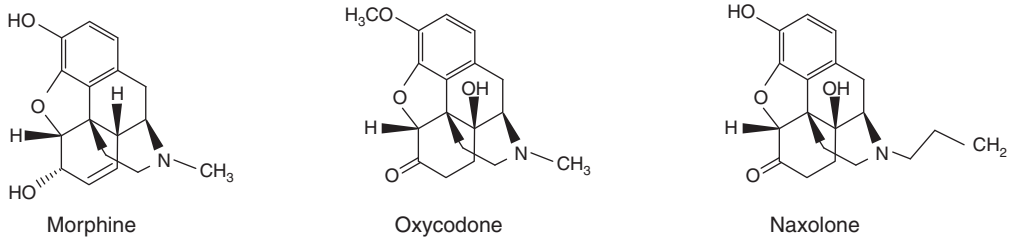


**Figure 1. Molecular formulas of morphine, OX and N.**

## 5. Pharmacodynamics

OX is a semisynthetic opioid alkaloid structurally similar to morphine (**Figure 1**); it acts as full opioid agonist, with affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g., intestine). The clinical efficacy of OX is similar to that of morphine, but OX is more potent with an equianalgesic ratio of 1:1.5 – 2 [10].

N is a competitive antagonist of opioid receptors inside and outside the central nervous system and, after systemic administration, it reverses both centrally and peripherally mediated opioid effects. N is a synthetic opioid antagonist of both central and peripheral opioid receptors with a remarkably higher affinity for mu-, delta- and kappa-receptors than opioid receptor agonists (**Figure 1**). Unlike other opioid antagonists, which do not completely inhibit the analgesic properties of opioids, N is devoid of any intrinsic agonist activity and antagonizes all actions of morphine. When administered intravenously, it acts centrally as a specific antidote in the management and reversal of overdoses caused by opioid agents, with a proven long-term safety profile and a safety over a wide dose range [11].

## 6. Pharmacokinetics

Oral administration theoretically allows selective blocking of intestinal opioid receptors without blocking the desired opioid effects, as long as hepatic first-pass capacity is not exceeded. The low systemic bioavailability due to marked hepatic first-pass metabolism allows for the low plasma levels and high enteric wall concentration. After parenteral administration, N plasma half life is ~ 1 h; the drug is metabolized in the liver and excreted in the urine. When orally administered in tablet form, N undergoes extensive elimination by hepatic first-pass. As a consequence, the systemic availability is low. The mean absolute bioavailability of N from the orally administered PR tablets ranged from 0.9% for the 5 mg dose to 2% for the 40, 80 and 120 mg doses [12]. Its principal metabolites are N-glucuronide, 6-Naloxol and its glucuronide [13]. Because of the pronounced first-pass metabolism, a clinically relevant systemic effect of N after its oral administration is unlikely; on the other hand, oral N may allow selective blockade of intestinal opioid receptors. Due to the local competitive antagonism of the opioid receptor in the gut, N reduces the bowel function disorders that are typical for opioid treatment, without blocking the desired analgesic effects of opioids in the central nervous system [13].

When orally administered, OX is readily absorbed, and its bioavailability ranges from 60 to 87%, which is higher than the 20 – 40% for morphine. OX has an elimination half life of ~ 3 h and is extensively metabolized in the liver, mainly via CYP3A4 to the inactive metabolite noroxycodone (47% of the dose), by 6-keto reduction to the most likely inactive metabolites, α- and β-oxycodol (8% of the dose), and via CYP2D6 to the active metabolite oxymorphone (11% of the dose), which has some analgesic activity but is present in the plasma in a conjugated form and in low concentrations. Thus, the parent drug exerts the major central opioid effects, with negligible contribution from its circulating oxidative and reductive metabolites. OX and its metabolites are excreted in the urine [10].

PR OXN is a prolonged-release fixed combination. The release of OX from PR formulation tablets is biphasic with an initial relatively fast release providing an early onset of analgesia, followed by a more controlled release which determines the 12 h duration of action. The mean apparent elimination half life of PR OX is 4.5 h, which leads to steady-state being achieved in about 1 day. The mean absolute bioavailability of N from orally administered PR tablets was found to be very low, ranging from 0.9% for the 5 mg dose to 2% for the 40, 80 and 120 mg doses, based on area under the concentration–time curve (AUCt) values; the pharmacokinetics of N were linear across the range of oral doses [13]. A study compared pharmacokinetics data from a single-dose study and a multiple-dose bioequivalence study of fixed-dose combination PR OXN versus separate formulations of PR OX and PR N. Both in the single-dose and multiple-dose steady-state bioequivalence studies, the mean plasma OX concentration–time curves for PR OX and PR OXN were similar; there were no statistically significant differences between the treatments, indicating that the coadministration of PR OX and PR N in a fixed-dose combination (PR OXN) would not significantly affect the bioavailability of either of its constituents [6].

## 7. Clinical efficacy

Three studies were performed in patients with low back pain and with chronic pain of different origins. A randomized,

double-blind, placebo- and active-controlled, parallel-group study was designed in 463 patients with moderate-to-severe low back pain. Doses of OX were in the range of 20 – 40 mg/day. The active control group was included to compare the analgesic efficacy and bowel function of PR OXN with PR OX. The analgesic efficacy was measured as the time from the initial dose of study medication to multiple pain events, corresponding to inadequate analgesia. The number of recurrent pain events was significantly longer in the PR OXN group compared with placebo. PR OXN reduced the risk of pain events by 42% compared with placebo. The appearance of pain events was comparable for PR OXN as against PR OX, confirming that the addition of N to OX in a combination tablet did not negatively affect analgesic efficacy of the opioid. In constipated patients with high bowel function index, complete spontaneous bowel movement significantly increased with PR OXN and was associated with lower use of laxative in comparison with PR OX group [14].

In a randomized, double-blind, double-dummy 12-week trial of 322 patients with chronic non-cancer pain, PR OXN and PR OX were compared, after a run-in phase with doses of PR OX ranging 20 – 50 mg/day. A significant improvement in bowel function index, less use of laxatives and complete spontaneous bowel movements were reported with PR OXN in comparison with PR OX, without compromising analgesia [15].

In another randomized, double-blind, double-dummy, parallel-group multicenter study the impact of PR OXN for patients with OIC having moderate-to-severe, nonmalignant pain, was assessed. Patients were previously converted to PR OX and titrated to an effective analgesic dose. A total of 265 patients on a stable PR OX of 60 – 80 mg/day and with OIC were included in the full analysis population to receive PR OXN or PR OX. After 1 week of treatment, patients receiving PR OXN showed a significant improvement in bowel function compared with those in the PR OX as measured by bowel function index. After 4 weeks of treatment, patients receiving PR OXN had more complete spontaneous bowel movements per week and a lower laxative intake compared with PR OX patients. Improvements in bowel function were achieved without loss of analgesic efficacy as pain intensity scores were comparable among the groups and consistent for the duration of the study [16].

Only one study was performed in cancer patients. A total of 185 patients were assessed in a randomized, double-blind, active controlled with PR OX, double-dummy, parallel-group study [17]. Previous opioid and laxative medications were stopped and patients were randomized to receive PR OXN or PR OX during the double-blind, double-dummy phase. Patients were titrated up to 120 mg/day of PR OXN or PR OX. OX was available as rescue analgesic drug, and bisacodyl as laxative rescue medication. Patients requiring higher doses than 120 mg/day were withdrawn from the study. After 4 weeks, mean bowel function index was significantly lower with PR OXN and total laxative intake was 20% lower. The brief pain inventory short-form scores, the use of analgesic rescue doses, quality of life, rate of discontinuation as well as adverse effects were comparable.

## 8. Pooled analysis

The two randomized 12-week, double-blind, parallel-group, multicenter studies [14,15] comparing PR OXN and PR OX alone on symptoms of opioid-induced bowel dysfunction in patients with moderate-to-severe nonmalignant pain were prospectively designed to be pooled, and the primary outcome measure of the pooled analysis was to demonstrate noninferiority in 12-week analgesic efficacy of PR OXN versus PR OX alone. This pooled analysis demonstrated that during a 12-week period, PR OXN provided analgesia that was as effective as PR OX alone, as indicated by the noninferiority of PR OXN versus PR OX in mean pain intensity, and a low and comparable use of supplemental analgesic medication in both treatment arms. Of interest, patients receiving PR OXN demonstrated clinically significant improvements in OIC, and there was also a significantly reduced use of laxatives in the first 4 weeks of the study in patients who received PR OXN compared with those who received PR OX alone [18].

## 9. Safety and tolerability

In general, controlled studies have demonstrated that PR OXN is safe and well tolerated. In the study by Vondrackova *et al.* [14], most adverse effects were mild or moderate in intensity and the incidence of severe adverse effects was low. The most frequent adverse effect leading to discontinuation was nausea. Severe adverse effects were slightly more frequently reported in PR OXN group than in PR OX group. In the study by Simpson *et al.* [15], the incidence of adverse effects was similar between the two groups. There were fewer gastrointestinal adverse effects, including nausea, vomiting, abdominal pain and dyspepsia in the PR OXN group, and mean duration of treatment-related diarrhea was slightly shorter in the PR OXN group. A total of 12 patients (9 in the PR OXN group and 3 in the PR OX group) experienced serious adverse effects. Opioid withdrawal was observed in two patients, one for each group. Löwenstein *et al.* [16] reported more adverse effects in the PR OXN group than the PR OX group. This was attributed to the higher incidence of abdominal pain, as a consequence of an increase in gut motility.

In the study of cancer patients [17], the proportion of patients who experienced adverse effects or severe adverse events was generally similar for PR OXN and PR OX groups.

## 10. Open-label extension studies

A 4-week postmarketing surveillance study of more than 7,000 patients with cancer and non-cancer pain receiving

low doses of PR OXN showed that bowel function and quality of life markedly improved [19]. In a 4-week study, PR OXN has been also reported to be effective in about 1,500 patients with neuropathic pain, maintaining normal bowel function and improving quality of life [20]. In a 1-year extension study of these two double-blind studies, patients with chronic pain received 20 – 120 mg doses of PR OXN. Results from these open-label extension studies over 12 months of treatment have demonstrated the long-term efficacy and tolerability of PR OXN in the treatment of chronic non-cancer pain. Patients experienced clinically relevant improvements in OIC, while receiving effective analgesic therapy [21]. Limited data are available in cancer pain. In the only existing controlled study, PR OXN has been shown to provide superior bowel function compared with prolonged release PR OX without compromising analgesic efficacy or safety. Maximum doses were 120/60 mg/day that is in the range of opioid requirements of many cancer patients [13]. This data was confirmed in an open-label exploratory study of cancer patients with OIC who were switched to PR OXN at a maximum daily dose of 40/20 mg. During a 2-week period of observation, bowel function index as well as stool consistency significantly improved. Five patients did not obtain pain relief at that dose and were switched to other opioids [22].

## 11. Regulatory affairs

PR OXN has been launched in Germany in 2006 via an expedited approval procedure. In 2012, it is available in more than 20 countries with proven efficacy and tolerability. Real-life experience with PR OXN is well documented and thousands of patients have taken advantage from this therapy. A recent research [23] performed by IMS demonstrated that in Italy more than 157,000 patients have been treated with OXN during the period from January 2011 to July 2012.

## 12. Expert opinion

PR OXN offers a unique and specific mechanism to control OIC in patients receiving chronic opioid therapy. This combination has the potential advantage of preventing OIC, particularly in subgroups of population, like elderly or advanced cancer patients. This approach can decrease the use of laxatives and additional medications, which represent a burden for patients presenting comorbidities requiring multiple medications.

There is a good evidence that PR OXN is effective in reducing OIC, while maintaining analgesia in patients with chronic pain. Traditional controlled studies demonstrated the efficacy and safety of this combination, with an improvement in bowel function and a substantial reduction in the use of laxatives. This has been proved by reanalysis of larger data and long-term studies [24]. Moreover, PR OXN was estimated to be a cost-effective option for treating patients with severe nonmalignant pain and OIC. Cost effectiveness of PR OXN and PR OX was compared in patients with moderate-to-severe nonmalignant pain and OIC from a cohort model used data from a Phase III randomized, controlled trial. It calculated the cost difference between treatments by combining the cost of pain therapy with costs of laxatives and other resources that were used to manage constipated patients. SF-36 scores were converted into EQ-5D utility values to calculate the quality-adjusted life year. Direct treatment costs were slightly higher for patients treated with PR OXN than for those treated with PR OX, but patients treated with PR OXN experienced a quality of life gain, and had an incremental cost-effectiveness ratio considerably below thresholds commonly applied in the United Kingdom [25].

PR OXN tablets provide equivalent analgesia to that of OX CR tablets of the same OX dose, with a similar adverse-effect profile. Adding the N component reduces, but does not eliminate, the prevalence of constipation. Compared with PR OX, the number needed to treat (NNT) (for one person using opioids continuously to avoid constipation) was about 4 for people with existing OIC (after 4 weeks), and about 14 for people not selected for constipation symptoms (after 12 weeks). Areas of uncertainty include efficacy data regarding analgesia and constipation from 12-week randomized controlled trials. Longer-term data (up to 52 weeks) are from uncontrolled trials. The tablets have not been compared with a regimen of OX and prophylactic laxatives.

As the studies in non-cancer pain are limited to a dose range of up to 80/40 mg of PR OXN, further research on higher doses would be recommended [5,6,14-16]. New strengths have been developed recently, which may allow for the use of larger doses. Actually, the maximal licensed daily dose is 80/40 mg/day. Doses were extended up to 120/60 mg/day in cancer patients, without reporting loss of analgesia [17]. In cancer patients it is often necessary to use high doses of opioids like OX. In an acute palliative care unit, about 20% of patients require doses of OX higher than 240 mg/day [26]. As there are no data about such high doses with PR OXN, potentially, when opioid requirements became high, dosage could be rounded by PR OX dosing or a switch should ultimately take place. These aspects should be assessed in future studies. New generations of opioid antagonists are going to be developed in the near future. Studies are ongoing.

## Declaration of interest

Professor S Mercadante acted as expert, advisor or faculty speaker in the last year for the following companies: Prostrakan, TEVA, Molteni, Janssen and Grunenthal. A Giarratano has no competing interests to declare. The article was written independently with no funding; however, MundiPharma has paid the publishing processing costs for the authors.

## Bibliography


1. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333
2. Holzer P, Ahmedzai SH, Niederle N, et al. Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J Opioid Manag 2009;5:145-51
3. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007;61:1181-7
4. Mercadante S. Emerging drugs for cancer-related pain. Support Care Cancer 2011;19:1887-93
5. Meissner W, Schmidt U, Hartmann M, et al. Oral naloxone reverses opioid-associated constipation. Pain 2000;84:105-9
6. Smith K, Hopp M, Mundin G, et al. Single and multiple-dose pharmacokinetic evaluation of oxycodone and naloxone in an opioid agonist-antagonist prolonged-release combination in healthy adult volunteers. ClinTher 2008;30:2051-68
7. Smith K, Hopp M, Mundin G, et al. Naloxone as part of a prolonged release oxycodone/naloxone combination reduces oxycodone-induced slowing of gastrointestinal transit in healthy volunteers. Expert Opin Investig Drugs 2011;20:427-39
8. Meissner W, Leyendecker P, Mueller-Lissner S, et al. A randomized controlled study with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. Eur J Pain 2009;13:56-64
9. Nadstawek J, Leyendecker P, Hopp M, et al. Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain. Int J Clin Pract 2008;62:1159-67
10. Riley J, Eisenberg E, Muller-Schwefe G, et al. Oxycodone: a review of its use in the management of pain. Curr Med Res Opin 2008;24:175-92
11. Van Dorp EL, Yassen A, Dahan A. Naloxone treatment in opioidaddiction: the risks and benefits. Expert Opin Drug Saf 2007;6:125-32
12. Lalovic B, Phillips B, Risler LL, et al. Quantitative contribution of CYP2D6 and CYP3A to oxycodone metabolism in human liver and intestinal microsomes. Drug Metab Dispos 2004;32:447-54
13. Smith K, Hopp M, Mundin G, et al. Low absolute bioavailability of oral naloxone in healthy subjects. Int J Clin Pharmacol Ther 2012;50:360-7
14. 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 2008;9:1144-54
15. Simpson K, Leyendecker P, Hopp M, 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;24:3503-12
16. Löwenstein O, Leyendecker P, Hopp M, 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;10:531-43
17. Ahmedzai SH, Nauck F, Bar-Sela G, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Pall Med 2012;26:50-60
18. Löwenstein O, Leyendecker P, Lux EA, et al. Efficacy and safety of combined prolonged release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. BMC Clin Pharmacol 2010;10:12
19. Schutter U, Frunert S, Meyer C, et al. Innovative pain therapy with a fixed combination of prolonged-release oxycodone/naloxone: a large observational study under conditions of daily practice. Curr Med Res Opin 2010;26:1377-87
20. Hermanns K, Junker U, Nolte T. Prolonged-release oxycodone-naloxone in the treatment of neuropathic pain – results from a large observational study. Expert Opin Pharmacother 2012;13:299-311
21. Sandner-Kiesling A, Leydendecker F, Hopp M, et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. Int J Clin Pract 2010;64:763-74
22. Clemens KE, Quednau I, Klaschik E. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. Int J Clin Pract 2011;65:472-8
23. Ricerca IMS Health – Patients on Drug Targin – metodo LRX (Longitudinal Prescription) 2012
24. Clemens KE, Mikus G. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: review of efficacy and safety data in the treatment of patients experiencing chronic pain. Expert Opin Pharmacother 2010;11:297-310
25. Dunlop W, Uhl R, Khan I, et al. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: a UK cost-utility analysis. J Med Econ 2012;15:564-75
26. Mercadante S, Ferrera P, David F, Casuccio A. The use of high doses of oxycodone in an acute palliative care unit. Am J Hosp Palliat Care 2011;28:242-4


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