Treatment With Prolonged-Release Oxycodone/Naloxone Improves Pain Relief and Opioid-Induced Constipation Compared With Prolonged-Release Oxycodone in Patients With Chronic Severe Pain and Laxative-Refractory Constipation

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ABSTRACT

Purpose: Laxative-refractory opioid-induced constipation (OIC) is defined as OIC despite using 2 laxatives with a different mechanism of action (based on the Anatomical Therapeutic Chemical Classification System level 4 term [contact laxatives, osmotically acting laxatives, softeners/emollients, enemas, and others]). OIC has a significant impact on the treatment and quality of life of patients with severe chronic pain. This noninterventional, observational, real-life study in Belgium investigated the efficacy of prolonged-release oxycodone/naloxone combination (PR OXN) treatment regarding pain relief and OIC compared with previous prolonged-release oxycodone (PR OXY) treatment for laxative-refractory OIC in daily clinical practice.

Methods: Laxative-refractory OIC patients with severe chronic pain were treated with PR OXN for 12 weeks (3 visits). Pain relief (assessed on a numerical rating scale) and OIC (assessed by using the Bowel Function Index [BFI]) were evaluated at each visit. A responder was defined as a patient who had: (1) no worsening of pain at the last visit compared with visit 1 or a numerical rating scale ≤4 at visit 3/last visit; and (2) a reduction in BFI ≥12 units at visit 3/last visit compared with visit 1; or (3) a BFI ≤28.8 at visit 3/last visit.

Findings: Sixty-eight laxative-refractory OIC patients with severe chronic pain (mean (sd) age 59.8 (13.3) years, 67.6% female and 91.2% non-malignant pain) were treated for 91 days with PR OXN (median daily dose, 20 mg). Treatment with PR OXN resulted in a significant and clinically relevant decrease of pain of 2.1 units (P < 0.001; 95% CI, 1.66–2.54) and of BFI by 48.5 units (P < 0.001; 95% CI, 44.4–52.7) compared with PR OXY treatment; use of laxatives was also significantly reduced (P < 0.001). Approximately 95% of patients were responders, and quality of life (as measured by using the EQ-5D) improved significantly. Adverse events were opioid related, and PR OXN treatment was well tolerated.

Implications: Treatment with PR OXN resulted in a significant and clinically relevant reduction in OIC compared with previous PR OXY treatment for these patients with severe chronic pain and laxative-refractory OIC. Treatment with PR OXN also resulted in a significant improvement in pain relief and quality of life. ClinicalTrials.gov identifier: NCT01710917. (Clin Ther. 2015;37:784–792) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: laxative refractory, laxatives, opioid-induced constipation, pain, quality of life.
INTRODUCTION

Opioids are widely used for the treatment of patients with severe chronic pain. However, adverse drug reactions associated with the use of opioids, particularly opioid-induced bowel dysfunction, can be problematic and severely affect quality of life. Opioid-induced constipation (OIC) is the most distressing symptom of opioid-induced bowel dysfunction and occurs in ~40% of opioid-treated patients. In contrast to opioid-related adverse effects mediated through the central opioid receptors, which occur at the start of treatment and usually rapidly lessen, OIC is mediated through intestinal opioid receptors and often persists throughout opioid treatment with no decline in intensity. OIC is the most troublesome opioid-related adverse effect reported by patients, resulting in reduction or discontinuation of treatment in one third of opioid-treated patients. Laxatives are the most common drugs used for relieving OIC. However, because laxatives do not address the underlying mechanisms of OIC, they are insufficiently effective in the majority of patients experiencing this condition. Moreover, there are no direct comparative data on different laxatives in the prevention or treatment of OIC, resulting in a lack of generally accepted guidelines regarding laxative use for this condition.

One strategy to minimize or prevent OIC while maintaining analgesic efficacy is blocking intestinal opioid receptors while allowing the activation of central opioid receptors. To this end, a prolonged-release tablet consisting of oxycodone and naloxone (PR OXN) in a 2:1 ratio was developed. Oxycodone has been shown to be an effective analgesic in various types of pain. Naloxone is an opioid receptor antagonist with low systemic bioavailability (<3%) primarily used as an injectable solution for the treatment of opioid overdose by its antagonizing effect on central opioid receptors. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, thereby counteracting OIC, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence on the central analgesic effect of oxycodone.

Several randomized controlled studies have reported on the comparable analgesic efficacy of PR OXN and prolonged-release oxycodone (PR OXY), with a significant and clinically relevant improvement in OIC with PR OXN compared with PR OXY in various types of pain even after long-term treatment. The frequency of adverse events was similar between PR OXN and PR OXY treatments. This outcome was confirmed in daily clinical practice in Germany for patients with a variety of pain etiologies.

PR OXN is indicated for the treatment of severe pain that can only be adequately managed with opioid analgesics. In Belgium, reimbursement for PR OXN is strictly limited to patients who have been treated with PR OXY for at least the last 30 days before PR OXN treatment and who are experiencing laxative-refractory OIC; this form is defined as OIC despite the use of at least 2 laxatives with different mechanisms of action (based on the Anatomical Therapeutic Chemical [ATC] Classification System level 4 term [e.g., contact laxatives, osmotically acting laxatives, softeners/emollients, enemas, and others] during previous PR OXY treatment.

The present real-life study was requested by the Belgian reimbursement authorities to investigate the efficacy of PR OXN in terms of both pain relief and OIC in chronic pain patients eligible for PR OXN reimbursement in Belgium. In addition to evaluation of efficacy regarding pain relief and OIC use of laxatives and analgesic rescue medication, quality of life and safety during PR OXN treatment compared with the previous PR OXY treatment were evaluated.

PATIENTS AND METHODS

Study Design

This noninterventional, observational, real-life study was designed to evaluate the pain relief and OIC of PR OXN treatment in daily practice in patients with chronic severe pain compared with previous PR OXY treatment. PR OXN treatment was started at visit 1. The study was performed by using electronic case record forms, and all parameters collected at visit 1 reflected the PR OXY treatment. Evaluations were performed during 2 follow-up visits. Visit 2 was scheduled after PR OXN dose titration, and visit 3 was scheduled at least 12 weeks after visit 1.

The study was conducted in accordance with Belgian and European health law and controlled drug regulations.

Patients

Patients enrolled in the present study met the reimbursement conditions for PR OXN in Belgium as well as the summary of product characteristics for
PR OXN. In Belgium, patients are eligible for reimbursement if they meet the following conditions: (1) all patients had to be aged ≥18 years, with a documented history of severe pain requiring around-the-clock opioid therapy, treated with PR OXY for at least 30 days with insufficient pain relief and/or unacceptable adverse effects; and (2) all patients had to be experiencing OIC (Bowel Function Index [BFI] ≥28.8 [discussed later in the Patients and Methods]) despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) during the previous PR OXY treatment.

Patients were excluded from the study if they met any of the following criteria (based on the summary of product characteristics): any history of hypersensitivity to oxycodone, naloxone, related products, or other ingredients; active alcohol or drug abuse and/or history of opioid abuse; participation in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry; surgery completed before the start of the study or planned surgery during the study that would influence pain or bowel function; or use of naloxone ≤30 days before the start of the study. Patients were also excluded if they had any of the following: diarrhea and/or opioid withdrawal; any situation in which opioids were contraindicated; or severe respiratory depression with hypoxia and/or hypercapnia, severe obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, nonopioid-induced paralytic ileus, and moderate to severe liver function impairments. Pregnant or breastfeeding women were also excluded.

Written informed consent was obtained from all patients for the anonymous use of the data.

**Medication**

PR OXN is available in oxycodone/naloxone tablets of 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg and was prescribed to the patients according to the summary of product characteristics. Patients were switched immediately from PR OXY to PR OXN with equal oxycodone doses. After the switch to PR OXN, the PR OXN dose could be titrated as needed. Use of laxatives and analgesic rescue medication as well as other comedication was allowed during PR OXN treatment (as in daily clinical practice) and was documented (yes/no was mandatory; type and dosage were optional).

**Study Assessments**

**Primary Parameter**

The primary parameter was the percentage of responders after 12 weeks of PR OXN treatment. The response was based on the parameters of pain and OIC. Pain was assessed at each visit by the physician on a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain). OIC was evaluated by the physician using the validated BFI. Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is the subject of European Patent Application Publication No. EP 1 860 988 and corresponding patents and applications in other countries. This index uses a numerical scale from 0 (easy/no difficulty) to 100 (severe difficulty/very strong) to record a patient’s subjective assessment of 3 items related to OIC: ease of defecation, feeling of incomplete bowel evacuation, and personal judgment regarding OIC. The BFI is calculated as the arithmetic mean of the scores for these 3 items. A lower score indicates a better bowel function; a score of ≤28.8 is considered a normal bowel function with respect to OIC, and a BFI change of ≥12 points is considered a clinically relevant change.

**Responders**

A patient was defined as a responder if the patient had: (1) no worsening of pain (NRS increase ≤1 unit at visit 3/last visit compared with visit 1 or an NRS ≤4 at visit 3/last visit; and (2) had a reduction in BFI of ≥12 units at the last visit compared with visit 1 or a BFI ≤28.8 at visit 3/last visit.

**Secondary Parameters**

Secondary parameters included the use of laxatives and analgesic rescue medication, evaluation of the quality of life, and safety assessments during PR OXN treatment compared with the previous PR OXY treatment.

Laxative use was assessed by asking if the patient had used laxatives in the 7 days before each study visit (yes or no); information on whether laxative use had increased/decreased or remained constant compared with the previous visit was also registered (decrease/constant/increase). If laxatives were used in the 7 days before the study visit, information regarding type, dose, and frequency of the used laxatives was optional due to the noninterventional character of the study. The percentage of patients using laxatives in the
7 days before each visit and the percentages of patients reporting increased/decreased/stable laxative use at visits 2 and 3 compared with visit 1 were calculated.

The assessment of the use of analgesic rescue medication was similar to the assessment of laxative use.

The patient’s quality of life was evaluated by using the standardized EQ-5D questionnaire. The EQ-5D score and EQ-5D visual analog scale (VAS) health score were recorded at visit 1 and at the last visit. A derived EQ-5D score was calculated from the 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as the absolute change in EQ-5D score and EQ-5D VAS health score between the last visit and visit 1.

Safety assessments consisted of monitoring and recording all serious adverse events (AEs) and adverse reactions at all visits.

**Statistical Analysis**

For the efficacy parameters, the analyses were performed for all patients meeting the inclusion criteria who received at least 1 dose of PR OXN treatment and who had at least 1 postdose efficacy evaluation (ie, the full analysis population). Patients using laxatives during the 30-day PR OXY treatment were included in this full analysis. Because patients were not asked proactively about laxative treatment before starting the study, and because the laxative use during the last 7 days was evaluated at the consecutive visits, a decision was made to also analyze the primary parameter for patients who used laxatives in the 7 days instead of 30 days before study inclusion (ie, the per-protocol population). The safety analysis was performed for all patients who had received at least 1 dose of study medication and had at least 1 safety assessment after the last dose (safety population). Descriptive statistics of all demographic characteristics, baseline variables, and study parameters were provided overall. Continuous data were summarized according to their mean, SDs, 95% CIs of the mean, median, and minimum and maximum. Categorical and ordinal data were summarized according to frequency and percentages. No imputation of missing data was performed.

A paired t test was used to test if there was a change in mean pain NRS, BFI, and EQ-5D score between the first and last visits. The McNemar test for paired data was used to determine if there was a change in use of laxatives or use of analgesic rescue medication between the first and the last visits. The effect of the treatment time on changes in mean BFI scores was studied in more detail by using linear mixed effect models. All statistical tests were performed by using a 2-sided significance level of 5%.

**RESULTS**

A total of 68 patients were included in the full analysis population (Figure 1). Approximately 91% of the patients (62 of 68) completed the study. Three patients (4.4%) discontinued of their own choice: 1 patient stopped due to an AE, and 2 patients (2.9%) discontinued for other reasons. For 3 subjects, no laxative intake for the last 7 days was documented, and 65 patients were thus included in the per-protocol analysis.

Table 1 displays the data for age, sex, and pain diagnoses for enrolled patients. The median study duration was 91 days (range, 7–127 days), with 37.5 days (range, 3–85 days) for visit 2 (dose titration) and 91 days for visit 3 (range, 39–127 days). These variations in durations were due to the noninterventional design of the study. The median dose of PR OXY treatment used before the start of the study (visit 1) was 20 mg (range, 5–360 mg). The median prescribed dose of PR OXN at visit 1 was similar to that of PR OXY (20 mg [range, 10–360 mg]). At visits 2 and 3, the median dose of PR OXN remained stable at 20 mg (range, 10–360 mg).

**Efficacy of PR OXN Treatment with Regard to Pain Relief**

The pain NRS was significantly reduced ($P < 0.001$) on average 2.1 units (95% CI, 1.66–2.54) between visit 1 (mean, 6.8 [1.5]) and visit 3 (mean, 4.6 [1.5]) (Figure 2). The mean pain NRS was also significantly decreased over time during PR OXN treatment to 3.8 after 18 weeks.

**Efficacy of PR OXN Treatment with Regard to OIC**

The BFI was significantly reduced ($P < 0.001$) on average 48.5 units (95% CI, 44.4 to 52.7) between visit 1 (mean, 70.8 [16.2]) and visit 3 (mean, 21.3 [13.2]) (Figure 3). The BFI significantly improved ($P < 0.001$) on average 3.4 units (95% CI, −3.8 to −3.0) per week during PR OXN treatment. This improvement on the BFI was clinically relevant, with
an average of 13.6 units (95% CI, 12 to 15.2) after 4 weeks of PR OXN treatment. After 6 weeks of PR OXN treatment, the average BFI was <28.8, and thus patients were considered no longer constipated.

Efficacy of PR OXN Treatment in Terms of Responders

The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage of responders after 12 weeks of PR OXN treatment compared with the previous PR OXY treatment. Data for 1 and 2 patients were missing for the full analysis and per-protocol populations, respectively (Figure 1, primary parameter). Among the full analysis population, 58 of 61 patients were qualified as responders (95.1% [95% CI, 86.0–98.9]); for the per-protocol population, 55 of 58 patients (94.8% [95% CI, 85.3–98.8]) were qualified as responders.

Use of Laxatives

The number of patients using laxatives in the 7 days before each visit decreased significantly from 65 patients (95.6%) at study start to 24 patients (38.7%) at visit 3 (McNemar test $\chi^2(1) = 37.0$, $P < 0.001$) (Table II).

The optional field for type of laxative was registered for 32 of 65 patients at visit 1; the majority of these patients (73%) used polyethylene glycol; 30%, bisacodyl; 17%, sodium picosulfate; 17%, senna; 8%, lactulose; and 8%, rectal laxatives. The sum of these percentages is >100% because >1 laxative could be registered.

Table I. Baseline characteristics of the patients (N = 68, full analysis population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>59.8 (13.3)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (32.4)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (67.6)</td>
</tr>
<tr>
<td>Pain diagnosis, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Nonmalignant*</td>
<td>62 (91.2)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>19 (30.6)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Low back pain</td>
<td>26 (41.9)</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2.9)</td>
</tr>
</tbody>
</table>

*For patients with nonmalignant pain, multiple diagnoses were possible.
Within the group of 41 patients using laxatives at visit 2, a total of 37 patients (90.2%) reported a decreased use of laxatives in the last 7 days compared with the preceding PR OXY treatment. Of the 24 patients using laxatives at visit 3, a total of 20 patients (83.3%) reported a decreased use of laxatives in the last 7 days compared with the preceding PR OXY treatment.

Use of Analgesic Rescue Medication

The number of patients using analgesic rescue medication in the 7 days before each study visit decreased significantly from 44 patients (64.7%) at study start to 26 patients (41.9%) at visit 3 (McNemar test $\chi^2(1) = 13.1, P < 0.001$). The optional field for type of rescue medication was registered for 28 of 44 patients, 19 of 37 patients, and 15 of 26 patients at visits 1, 2, and 3, respectively. The majority of these patients (visit 1, 68%; visit 2, 63%; and visit 3, 66%) used oxycodone as rescue medication.

Quality of Life

The EQ-5D score increased significantly (on average) 0.275 unit (95% CI, 0.202–0.347) between visit 1 (mean, 0.247 [0.233]) and the last visit (mean, 0.522 [0.275]) ($P < 0.001$). The EQ-5D VAS health score increased significantly (on average) 25.2 units (95% CI, 20.1–30.3) between visit 1 (mean, 33.0 [13.0]) and the last visit (mean, 58.2 [16.8]) ($P < 0.001$).

Safety Analysis

Only 2 patients (2.9%) reported an AE. One patient reported euphoria and drowsiness at visit 2. The other patient had an epileptic seizure after visit 2; however, this episode was considered to be unrelated to PR OXN treatment.

AEs were of average intensity and were pharmaco-logically treated, leading to elimination of the AE. No serious AEs were reported throughout the study.

DISCUSSION

The present study, requested by the Belgian reimburse-ment authorities, evaluated the efficacy of PR OXN in terms of pain relief and OIC in 68 patients with chronic pain who were treated with PR OXY during at least the last 30 days before PR OXN treatment and who experienced OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term).

To the best of our knowledge, this is the only non-interventional study of opioid treatment in which laxative use was documented before and during the treatment.

This study found that PR OXN was superior to PR OXY in terms of pain relief, OIC, and quality of life in patients with chronic pain previously treated with PR OXY and experiencing OIC despite the use of at least 2 different laxatives. The mean pain NRS was significantly reduced, on average, 2.1 units during treatment with PR OXN, comparable to other studies previously
demonstrating similar analgesic efficacy of PR OXN and PR OXY even after long-term treatment with PR OXN.\textsuperscript{4,9,12–15} The median PR OXN daily dose of 20 mg remained constant throughout the study and was equal to the PR OXY dose during the preceding PR OXY treatment. Moreover, the use of analgesic rescue medication decreased significantly during PR OXN treatment compared with the preceding PR OXY treatment. The observed improved pain relief during PR OXN treatment can therefore not be explained by an increased dose or increased use of analgesic rescue medication and is probably related to the improved OIC during PR OXN treatment.

This is the first noninterventional study in which the effect of PR OXN on OIC was evaluated by using 2 parameters: BFI and laxative use. The BFI exhibited a statistically significant and clinically relevant improvement of 48.5 points from visit 1 to the last visit. A change in BFI of $\geq 12$ points has proven to be related to clinically meaningful changes in bowel habits in patients with OIC.\textsuperscript{18} This study confirmed that after 4 weeks of treatment with PR OXN, a clinically relevant improvement in OIC was attained in patients experiencing laxative-refractory OIC. The average BFI was $< 28.8$ after 6 weeks of PR OXN treatment, indicating that most patients were no longer constipated despite the opioid treatment.\textsuperscript{19}

In addition to the BFI, PR OXN efficacy regarding OIC was investigated by comparing the use of laxatives between the previous PR OXY treatment and PR OXN treatment. The number of patients using laxatives declined significantly during PR OXN treatment compared with PR OXY treatment. If laxatives were needed, the majority of patients using laxatives during PR OXN treatment indicated decreased laxative use during PR OXY treatment. Therefore, the improvement in OIC observed during PR OXN treatment cannot be explained by an increased use of laxatives. This supports the rationale that PR OXN treatment counteracts OIC through mechanisms other than those of laxatives and that PR OXN addresses the underlying mechanism of OIC. The results of this noninterventional study are similar to results of a pooled analysis of laxative-refractory OIC patients from studies with PR OXN with respect to BFI and laxative use.\textsuperscript{20} This pooled analysis showed that PR OXN significantly improved bowel function and reduced the use of laxatives in patients with OIC who were previously unresponsive to at least 2 different classes of laxatives.

PR OXN also provided effective analgesia for patients with moderate to severe cancer-related and non–cancer-related pain. The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage of responders after PR OXN treatment compared with the percentages from the previous PR OXY treatment. The percentage of responders was 95.1\% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced a pain NRS score $\leq 4$ or improved pain relief in the absence of OIC (BFI $\leq 28.8$) or with a clinical improvement in OIC (BFI improvement $\geq 12$ units) compared with the preceding PR OXY treatment.

Quality of life improved significantly during PR OXN treatment. The overall EQ-5D score and EQ-5D VAS health score increased significantly, on average, 0.275 and 25.2 units, respectively, after 12 weeks of PR OXN treatment compared with PR OXY treatment. This

### Table II. Laxative use in the 7 days before the study visit. Data are given as no. (%)。

<table>
<thead>
<tr>
<th>Laxative Use</th>
<th>Visit 1*</th>
<th>Visit 2†</th>
<th>Visit 3‡</th>
<th>Last Visit†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/no</td>
<td>65/3 (95.6/4.4)</td>
<td>41/26 (60.3/38.2)</td>
<td>24/38 (38.7/61.3)</td>
<td>26/42 (38.2/61.8)</td>
</tr>
<tr>
<td>Decrease/constant/increased‡</td>
<td>NA</td>
<td>37/3/1 (90.2/7.3/2.4)</td>
<td>20/4/0 (83.3/16.7/0)</td>
<td>21/5/0 (80.8/19.2/0)</td>
</tr>
<tr>
<td>Missing data</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NA = not available.
* Laxative used in the last 7 days before study inclusion. These data are considered data for laxative use during the previous prolonged-release oxycodone (PR OXY) treatment.
† Laxative used in the last 7 days before study visit: yes/no and increased, decreased, or constant laxative use during prolonged-release oxycodone/naloxone combination treatment compared with the preceding PR OXY treatment.
‡ Decrease/constant/increased laxative use for patients who used laxatives during the preceding PR OXY treatment.
improved quality of life probably reflects the improved pain relief and OIC during PR OXN treatment and is consistent with the results of previous studies.4,16,21

PR OXN treatment was well tolerated in this study, and no serious AEs were reported. The frequency of AEs was lower compared with other studies, which can be explained by the observational design of the study.

Remarkably, 1 patient was directly switched from a daily dose of 360 mg of oxycodone to an equivalent dose of 360 mg/180 mg of oxycodone/naloxone. In current literature, daily doses of up to 240 mg/120 mg of oxycodone/naloxone have been described using a step-wise switch from oxycodone to oxycodone/naloxone with different outcomes.14,22 Close review of the patient’s records revealed that the patient responded well to the direct switch. Pain relief with oxycodone was comparable to pain relief with oxycodone/naloxone (pain NRS score was 3 throughout the 87-day treatment period). Moreover, no AEs were reported, the patient did not require any analgesic rescue medication or other concomitant medication, and a decrease in laxative medication was reported in addition to an improvement in bowel function after the switch from oxycodone to oxycodone/naloxone (BFI decreased from 46.7 to 0).

A noninterventional study has limitations, one of them being that we could not ensure that all data were documented in the database. This limitation was addressed by marking important parameters (eg, BFI, pain relief, laxative use yes/no, rescue medication yes/no) as mandatory fields in the electronic case record form; as a result, few data were missing for these fields.

Although keeping the inherent limitations of a noninterventional study in mind, the effects of PR OXN in real-life clinical practice in Belgium for those patients who were eligible for reimbursement found significant reductions in OIC during treatment of PR OXN in laxative-refractory OIC patients. The results of this real-life study confirmed the improvement seen in a pooled analysis from pivotal studies with PR OXN in a comparable patient group.20

CONCLUSIONS
In this real-life study in Belgium, patients with chronic severe pain and OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) experienced a significant improvement in pain relief, a significant and clinically relevant reduction in OIC, and a significant improvement in quality of life after PR OXN treatment compared with previous PR OXY treatment. The percentage of responders was 95.1% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced no pain or improved pain relief in the absence of OIC or with a clinical improvement in OIC compared with the preceding PR OXY treatment.

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CONFLICTS OF INTEREST
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outside the submitted work. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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