Cost-utility analysis of prolonged release oxycodone/naloxone for the treatment of patients with non-malignant moderate-to-severe pain and laxative refractory opioid induced constipation in The Netherlands

Gineke Koopmans-Klein
Yvonne J.B. van Megen
Will Dunlop
Maaike Dirckx
Frank J.P.M. Huygen

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ABSTRACT

Objective

To compare the cost effectiveness of prolonged release (PR) oxycodone/naloxone (OXN) and prolonged release oxycodone (PR OXY) in patients with moderate-to-severe pain of non-malignant origin suffering from laxative-refractory opioid induced constipation (OIC) from the perspective of the Dutch healthcare system.

Methods

The pharmaco-economic model was a cohort cost-utility model with constipated and non-constipated health states. It was adapted from a model which was previously used in non-malignant chronic pain in the UK context and published in 2012 by Dunlop et al.[1]. Data from a pooled analysis of two phase III randomized, controlled trials (RCTs) focusing on patients with non-malignant chronic moderate to severe pain and laxative refractory OIC under PR OXY treatment were used. Dutch costs data were used to calculate the cost difference between treatments in the model by combining the costs of pain therapy, costs of laxative use, costs of additional constipation treatments as well as costs of other resources used to manage constipation. The base case analysis was from a societal perspective, including societal costs. EuroQol-5 dimensions (EQ-5D) utility values for constipation were derived from a study performed in the Netherlands by Penning-van Beest et al.[2]. EQ-5D utility and disutility due to constipation were used to calculate the quality adjusted life year (QALY) gains. Deterministic and probabilistic sensitivity analyses were performed.

Results

The incremental cost of PR OXN versus PR OXY was €763 for the average treatment duration of 52 weeks per patient. PR OXN gave an incremental QALY gain of 0.110 per patient. The estimated incremental cost-effectiveness ratio (ICER) was €6,924 per QALY gained. Sensitivity and scenario analyses gave a maximum ICER of € 21,284 per QALY gained when increasing the probability of constipation in the PR OXN arm by 25%. Key drivers of the model are the utility value for non-constipated patients, the probability of constipation in the PR OXN arm and the mean daily dose of opioid per day. Probabilistic sensitivity analysis showed that PR OXN had approximately 96% probability of being cost effective at the €20,000 threshold.

Limitations

The main limitations of the analysis were the limited data of costs of constipation. These were obtained from a 2-round Delphi panel of 12 Dutch GPs and were therefore based on the perceptions of primary care physicians[3]. As indicated by Dunlop et al.[1], other

groups of healthcare professionals, like nurses and secondary care specialists treating constipation, may report different resource use and costs. A second limitation might be a possible lack of power of the Penning-van Beest study providing the utility scores and disutility[2]. Moreover, the health states were based on constipation, the most common side-effect of opioid treatment. However, PR OXN may counteract other aspects of opioid-induced bowel disorders (such as abdominal pain, cramping and bloating) that may require additional healthcare resources. It is therefore possible that a model examining these aspects on top of OIC may show a greater incremental QALY gain from PR OXN compared with PR OXY.

Conclusions

The present pharmaco-economic study demonstrated PR OXN was estimated to be a cost-effective option for treating patients with non-malignant moderate to severe pain and laxative-refractory OIC. Several sensitivity and scenario analyses show the robustness of the model.

INTRODUCTION

Opioids are an effective analgesic therapy recommended by the World Health Organization for a specific group of patients[4]. The WHO three-step analgesic ladder is used as a reference in several international guidelines, including the European Society for Medical Oncology (ESMO[5]), and the European Association for Palliative Care (EAPC[6]). Besides treatment of malignant pain opioids are also used in the treatment of severe nociceptive non-malignant pain[7].

Side effects of opioids are well known and often require a dose limitation, and sometimes a treatment discontinuation[8]. Constipation, nausea, somnolence/dizziness, dry mouth and respiratory depression remain commonly reported adverse events of opioid usage[9].

Opioid induced constipation (OIC) is defined as "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency"[10]. On top of impacting the correct intake of the opioid treatment, OIC has a major impact on patient's quality of life (QoL)[2,9,11-13] and can eventually lead to debilitating complications like external peri-anal thrombosis, anal fissures or rectum prolapse[14]. Therefore OIC is an additional burden especially for patients with chronic moderate-to-severe pain, a vulnerable group of patients [15-18].

In current practice the advice is to treat patients on opioid analgesics prophylactically with a laxative regime. In Dutch clinical practice this laxative regime consists of treatment with at least one laxative in an adequate dosage (e.g. macrogol plus electrolytes or lactulose) and if needed addition of a second laxative of a different therapeutic class (e.g. bisacodyl)[19]. However, some patients still experience OIC despite the use of this laxative regime and/or do not tolerate the adverse events of the laxative regime; i.e. patients with laxative-refractory OIC[20,21]. Current management of OIC episodes includes the symptomatic treatment with oral laxatives (osmotic laxatives, stimulant laxatives and stool softeners), rectal laxatives and lavements. Laxatives have been found to be ineffective to treat OIC[19,22]. Moreover, treatment with laxatives causes side effects and complications[10,23]. Opioid receptor antagonists like methylnaltrexone, naloxegol and naloxone are used for the pathophysiological treatment of OIC [24-26]. They inhibit binding of opioids to the opioid receptors in the gut, thereby preventing OIC[10,22].

PR OXN combines the strong opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. When administered orally, a reduction of constipation can be achieved due to a local action of naloxone in the gut without affecting pain relief by oxycodone[27-29]. PR OXN has proven equivalent analgesic efficacy to PR OXY with significant improvements in bowel function in chronic non-malignant pain[30-35] as well

as in moderate/severe malignant pain[36,37]. It is important to assess cost utility of PR OXN treatment for laxative-refractory patients, as treatment with PR OXN is more expensive than treatment with PR OXY.

The present publication describes the methodology and findings of a Dutch cost-utility analysis for PR OXN for patients with non-malignant moderate-to-severe pain who need treatment with an opioid to obtain adequate analgesia and laxative-refractory OIC.

METHODS

Patients and treatments

The model used data from a pooled analysis of two randomized, controlled, double-blind, parallel-group studies in non-malignant pain patients published in 2014 by Koopmans et al.[21]. This pooled analysis included 35 patients with non-malignant pain with OIC at study entry that was refractory to at least two laxatives with different modes of action (at least two laxatives of a different ATC-level 4 class). Patients completed randomized, double-blind treatment with PR OXN 20–120 mg/day for 12 weeks with an extension phase of up to 52 weeks. The primary objective of this pooled analysis was to evaluate bowel function in patients randomized to PR OXN who had OIC at study entry, despite the use of at least two different classes of laxatives. Assessment of bowel function was performed using the validated Bowel Function Index (BFI* (*Copyright for the BFI is owned by Mundipharma Laboratories GmbH, Switzerland 2002; the BFI is the subject of European Patent Application Publication No.EP1860988 and corresponding patents and applications in other countries)[38-40]. BFI score comprised the arithmetic mean score of three items rated on a numerical analogue scale (NAS) of 0–100: ease of defecation (0=easy/no difficulty to 100=severe difficulty), feeling of incomplete bowel evacuation (0=not at all to 100=very strong), and personal judgment of constipation (0=not at all to 100=very strong). Normal bowel function is defined as a score of ≤28.8; this was determined in a study that reported that 95% of non-constipated patients had a BFI score ≤28.8. BFI score was assessed at screening, start of double-blind treatment and end of double-blind treatment. Laxative use (bisacodyl and non-study laxatives) throughout the studies was documented. Full details of the study populations have been previously described[21,30-35]. The study showed statistically significant and clinically relevant improvements in bowel function following double-blind treatment with PR OXN. Mean (SD) reduction in BFI score was 23.3 [29.0] ($P \leq 0.0002$). Furthermore, the proportion of patients with a BFI score within normal range (≤28.8) increased from 8.6% at screening to 50.0% at Day 15 of PR OXN. While all patients used ≥2 laxatives of different classes at screening, during study treatment 36% stopped using laxatives ($P<0.001$). PR OXN provided effective analgesia, evidence by stable pain scores during study treatment,

and there were no unanticipated adverse events. The mean (sd) dose of oxycodone used was 54.5 (29.5) mg and was relatively stable, changing with 4.9 (12.5) mg from start of treatment to end of treatment.

Model structure and overview

A cohort cost-utility model was developed in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) with constipated and non-constipated health states. The model calculated the incremental cost-effectiveness ratio (ICER) defined as Δcost/Δeffectiveness, where effectiveness was defined in terms of quality adjusted life-years (QALY) gained[1]. Utility values were derived from an article by Penning-van Beest describing the impact of OIC on QoL, using the EQ-5D score[2]. Pain control was not included as a health state as based on the study data, it was assumed to be equal between treatments. The model included laxative use as patients treated with opioids require laxative treatment to prevent OIC. For this subpopulation of laxative-refractory OIC patients all patients in the oxycodone arm (PR OXY) are per definition treated with two laxatives of a different Anatomical Therapeutic Chemical (ATC) level 4 class (e.g. the ATC level 4 code of macrogol is A 06 AD 15) and for the PR OXN arm laxative use was based on the use of rescue laxative in the study by Koopmans et al. 2014[21]. Figure 1 shows the structure of the model.

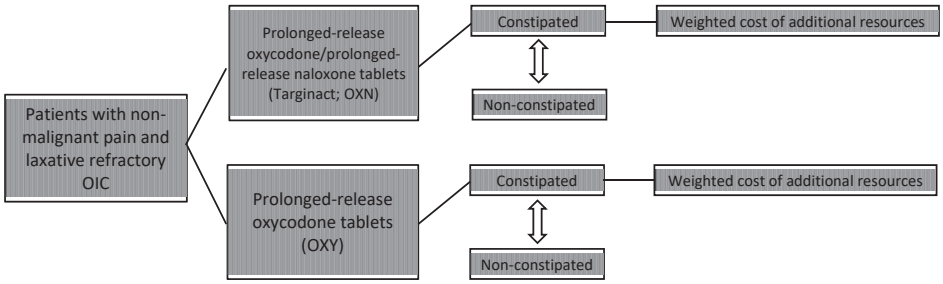

Figure 1: Model structure.

Most patients started in a constipated health state to mimic laxative-refractory OIC as well as the data from the pooled analysis. Over time patient movement occurred between the constipated and non-constipated health states, with the constipated health state incurring an additional cost. The model had weekly time intervals. The time horizon used in the base case analysis was 365 days, according to the average duration of treatment with PR OXY tablets in patients with non-malignant chronic pain. Cost and effects were not discounted owing to the time horizon being less than 1 year.

The following equations were used in the model:

Total cost of drug (laxative and pain treatment)

C_{OXN}=total cost of drug in treatment group over the treatment period for patients treated with PR OXN and C_{OXY}= total cost of drug in treatment group over the treatment period for patients treated with OXY. K=the expected duration of each treatment, which is estimated at 52 weeks, hence K=52.

D_{OXN} is the average weekly cost of PR OXN and D_{OXY} is the average weekly cost of PR OXY. Therefore, D_{OXN}=cost per mg of PR OXN x average (mean) dose (mg) PR OXN per day x 7 (days) and D_{OXY}=cost per mg of PR OXY x average (mean) dose (mg) PR OXY per day x 7 (days).

L_{OXN} is the average weekly cost of as needed bisacodyl use in the OXN treatment group. L_{OXN}=cost per mg bisacodyl x average (mean) dose (mg) bisacodyl per day x 7 (days). L_{OXY} is the average weekly cost of optimal laxative use in the OXY treatment group L_{OXY}=average cost of optimal laxative use per day x 7 days.

Hence, $C_{OXN} = K(D_{OXN}+ L_{OXN})$ and $C_{OXY}=K(D_{OXY}+L_{OXY})$

Resource use costs

Pi_{OXN} is the proportion of patients with constipation in the PR OXN treatment group at each week (i, i=week 1,2….,52) and Pi_{OXY} is the proportion of patients with constipation in the PR OXY treatment group at each week.

The total average weekly cost per patient of additional resource use is V, where V=average cost of additional resource use per constipated patient per week. Costs of additional resource use do not differ between patients in the PR OXN and PR OXY group. Therefore, using a half-cycle correction, the additional healthcare costs in the PR OXN treatment group (Z_{OXN}*) is given by:

$(P0_{OXN}+P1_{OXN})/2*V+(P1_{OXN}+P2_{OXN})/2*V+(P2_{OXN}+P3_{OXN})/2*V+….+(P51_{OXN}+P52_{OXN})/2*V$

And the additional healthcare costs in the PR OXY treatment group (Z_{OXY}*), using a half-cycle correction is given by:

$(P0_{OXY}+P1_{OXY})/2*V+(P1_{OXY}+P2_{OXY})/2*V+(P2_{OXY}+P3_{OXY})/2*V+….+(P51_{OXY}+P52_{OXY})/2*V$

The incremental cost is therefore $(C_{OXN}-C_{OXY})+(Z_{OXN}*-Z_{OXY}*)$

Utilities

If the utilities for the constipated patients in the PR OXN treatment group at each week are denoted

$U_{OIC, OXN}i$ then, the total QALY gain across all 52 weeks for the constipated patients in the PR OXN treatment group can be defined as $U_{OIC, OXN}$ is:

$U_{OIC, OXN}$ =((P0$_{OXN}$+P1 $_{OXN}$)/2*($U_{OIC, OXN}$0+ $U_{OIC, OXN}$1)/2)+(P1 $_{OXN}$+P2 $_{OXN}$)/2*($U_{OIC, OXN}$1+ $U_{OIC, OXN}$2)/2+(P2 $_{OXN}$+P3 $_{OXN}$)/2*($U_{OIC, OXN}$2+ $U_{OIC, OXN}$3)/2+….+(P51$_{OXN}$+P52$_{OXN}$)/2*($U_{OIC, OXN}$51+ $U_{OIC, OXN}$52)/2).

If the utilities for the non-constipated patients in the PR OXN treatment group at each week are denoted

$U_{non-OIC, OXN}$i then, the total QALY gain across all 52 weeks for the non-constipated patients in the PR OXN treatment group defined as $U_{non-OIC, OXN}$ is:

$U_{non-OIC, OXN}$ =(1-(P0$_{OXN}$+P1 $_{OXN}$)/2)*($U_{non-OIC, OXN}$0+ $U_{non-OIC, OXN}$1)/2)+(1-(P1 $_{OXN}$+P2 $_{OXN}$)/2)*($U_{non-OIC, OXN}$1+ $U_{non-OIC, OXN}$2)/2+(1-(P2 $_{OXN}$+P3 $_{OXN}$)/2)*($U_{non-OIC, OXN}$2+ $U_{non-OIC, OXN}$3)/2+….+(1-(P51$_{OXN}$+P52$_{OXN}$)/2)*($U_{non-OIC, OXN}$51+ $U_{non-OIC, OXN}$52)/2).

U_{OXN}*= $U_{OIC, OXN}$ + $U_{non-OIC, OXN}$

If the utilities for the constipated patients in the PR OXY treatment group at each week are denoted

$U_{OIC, OXY}$i then, the total QALY gain across all 52 weeks for the constipated patients in the PR OXN treatment group defined as $U_{OIC, OXY}$ is:

$U_{OIC, OXY}$ =((P0$_{OXY}$+P1 $_{OXY}$)/2*($U_{OIC, OXY}$0+ $U_{OIC, OXY}$1)/2)+(P1 $_{OXY}$+P2 $_{OXY}$)/2*($U_{OIC, OXY}$1+ $U_{OIC, OXY}$2)/2+(P2 $_{OXY}$+P3 $_{OXY}$)/2*($U_{OIC, OXY}$2+ $U_{OIC, OXY}$3)/2+….+(P51$_{OXY}$+P52$_{OXY}$)/2*($U_{OIC, OXY}$51+ $U_{OIC, OXY}$52)/2).

If the utilities for the non-constipated patients in the PR OXN treatment group at each week are denoted

$U_{non-OIC, OXY}$i then, the total QALY gain across all 52 weeks for the non-constipated patients in the PR OXN treatment group defined as $U_{non-OIC, OXY}$ is:

$U_{non-OIC, OXY}$ =(1-(P0$_{OXY}$+P1 $_{OXY}$)/2)*($U_{non-OIC, OXY}$0+ $U_{non-OIC, OXY}$1)/2)+(1-(P1 $_{OXY}$+P2 $_{OXY}$)/2)*($U_{non-OIC, OXY}$1+ $U_{non-OIC, OXY}$2)/2+(1-(P2 $_{OXY}$+P3 $_{OXY}$)/2)*($U_{non-OIC, OXY}$2+ $U_{non-OIC, OXY}$3)/2+….+(1-(P51$_{OXY}$+P52$_{OXY}$)/2)*($U_{non-OIC, OXY}$51+ $U_{non-OIC, OXY}$52)/2).

U_{OXY}*= $U_{OIC, OXY}$ + $U_{non-OIC, OXY}$

The ICER is therefore given by

((C_{OXN}-C_{OXY})+(Z_{OXN}*-Z_{OXY}*))/U_{OXN}*-U_{OXY}*

Model inputs

Cost inputs

Unit costs were based on the pharmacy purchase price (AIP) of each strength of PR OXN and PR OXY and were retrieved from the Dutch national list prices database (source:www.z-index.nl, January 2015)). The pack costs for PR OXN were €78.63 (90 tablets 5 mg), €106.50 (90 tablets 10 mg), €197.52 (90 tablets 20 mg) and €388.54 (90 tablets 40 mg).

The cost of PR OXY was a weighted average of the different available presentations (OxyContin® and its generic versions). The weight was based on the actual dispensed units of the different oxycodone strengths from the different manufacturers (source: www.farminform.nl). The weighted average pack costs for PR OXY were €3.73 (30 tablets 5 mg), €5.31 (30 tablets 10 mg), €9.09 (30 tablets 20 mg) and €40.87 (30 tablets 40 mg). The model used dispensed unit data for PR OXN and PR OXY to calculate a weighting that was then used to estimate cost per mg. The weightings applied were 29.7% (5 mg), 49.8% (10 mg), 17% (20 mg) and 3.5% (40 mg). It yielded average costs per mg of € 0.12 for OXN and € 0.02 for OXY (Table 1).

Table 1: Information for PR OXN and PR OXY weighted average price calculation used in the model

Strength	**Sales**	**OXN**			**OXY**		
mg opioid	**%**	**Pack size**	**AIP/pack**	**€/mg**	**Pack size**	**AIP/pack**	**€/mg**
5	29.7%	98	€78.63	€ 0.16	30	€ 3.73	€ 0.02
10	49.8%	98	€106.50	€ 0.11	30	€ 5.31	€ 0.02
20	17.0%	98	€197.52	€ 0.10	30	€ 9.09	€ 0.02
40	3.5%	98	€388.54	€ 0.10	30	€ 40.87	€ 0.03
Total	**100%**			**€ 0.12**			**€ 0.02**

The average daily dose of opioid during treatment of laxative-refractory patients was 54.5 mg (Koopmans et al.)[21,]. As opioid antagonist treatment does not interfere with pain relief this dose was used in both arms. The dose was multiplied with the average cost per mg of each drug to estimate the cost of opioid treatment in each arm of the model. The weighted cost per week of OXY was €7.62; the weighted cost per week of PR OXN was €46.69.

The average costs of laxative use for patients on PR OXN treatment was based on laxative costs derived from the Dutch national list prices database (Table 2; source:www.z-index.nl, January 2015) as well as laxative use from patient data (Koopmans et al.)[21]. 42.9% of laxative-refractory patients received 'as needed' bisacodyl, with an average daily dose of 4.32mg[21].

For patients on PR OXY treatment the average costs of laxative use were based on current Dutch practice and guidelines which recommend laxative treatment during opioid treatment for all patients. It was therefore assumed that 100% of patients were receiving the laxative treatment, being a combination of lactulose/movicolon+ bisacodyl on a daily basis[19,41]. The national public claims database user information showed that 11% of patients are using lactulose and 89% macrogol plus electrolytes (source: www.gipdatabank.nl). The average cost of optimal laxative use per day in the PR OXY arm was estimated using the weighted average cost of lactulose/macrogol combinations based on number of users derived from the national public claims database (GIP-databank) and medication costs from the national list prices database (Z-index) (Table 2). The corresponding weekly cost of laxatives in addition to opioid treatment were calculated was estimated at €0.09 with PR OXN and €2.11 with PR OXY.

A two-round Delphi panel including 24 Dutch GPs in first round and 12 Dutch GPs in second round showed that patients with laxative-refractory OIC regularly require treatments in addition to a laxative regime to temporarily obtain relief from OIC over time[3]. Moreover, patients with laxative-refractory OIC can suffer from complications caused by OIC. The medical resources, including additional laxatives, visits, diagnostic tests and procedures required to temporarily relieve OIC and to treat OIC complications as well as the frequency of additional required OIC treatment and the percentage of patients suffering from complications during an additional treatment for OIC were also collected in the Delphi panel. Costs for productivity losses and costs for transportation during periods with additional OIC treatments were also collected in the Delphi panel. Each item was multiplied with its unit cost to obtain the average total cost per additional OIC treatment. The costs of complications are linked with the number of additional OIC treatments needed and the average total cost for OIC complications.

Table 2: Average costs of laxative use per week for patients using OXN and OXY.

OXN	**% of patients using laxative**	**Average daily dose**	**Cost/unit (€)**	**Cost/day (€)**
Costs of Bisacodyl per day	42.9%	4.32mg	0.0073/mg	€ 0.0135
Total laxative cost with OXN per week				**€ 0.09**
OXY	**% of patients using laxative**	**MDD***	**Cost/unit (€)**	**Cost/day (€)**
Costs of Lactulose per day	11%	1 bag, 15 ml (12 g granules)	0.0146/ml	€ 0.024
Macrogol plus electrolytes per day	89%	1 bag, 25 ml	0.0092/ml	€ 0.205
Bisacodyl per day	100%	10mg	0.0073/mg	€ 0.073
Total laxative cost with OXY per day				€ 0.302
Total laxative cost with OXY per week				**€ 2.11**

*MDD=minimal daily dosage as per SmPC.

As the Dutch national guidelines on opioid treatment and OIC prevention have not changed significantly since 2008, the type and frequency of medical resources used obtained from the Delphi panel performed in 2008 were not updated[19,41]. The corresponding unit costs for visits and treatments in different settings were retrieved from the 2010 costing manual (2009 costs) and were inflated to 2014 using the evolution of the consumer price index (CPI), Health compound, between 2009 (102.55) and the most recent year available (2014: 105.88, factor 1.03) as per national guidelines. A further assumption was required in order to estimate the additional total cost of OIC on average per year.

Delphi-panel outcomes

On average, in the Delphi panel the experts reported that additional OIC treatment to temporarily relief OIC in laxative-refractory OIC patients was needed on average 6 (range 3.0-10.0) times over a 12 month period[3]. Most frequently reported resources for additional OIC treatment in laxative-refractory patients within the Delphi-panel were medications (up to 64%), GP (home) visits (up to 53%) and in hospital treatments (up to 30%). The corresponding cost of one additional OIC treatment course in constipated patients was estimated at €171.67 per additional OIC treatment; or €19.81 per week (Table 3)[3].

Table 3: Costs for additional OIC treatments, costs for OIC complications, costs of productivity loss and transport costs.

Cost item	€ / OIC per additional OIC treatment course	95% CI	€ / week*	95% CI
Total additional OIC treatment	**171.67**	**[129-215]**	**19.81**	**[15-25]**
Total OIC complications	**318.90**	**[204-434]**	**36.80**	**[24-50]**
Average cost of productivity loss caused by OIC, per additional OIC treatment	**107.32**	**[19-195]**	**12.38**	**[2-23]**
Average transport costs home-hospital, per additional OIC treatment (due to additional OIC treatments and treatment of OIC complications)	**2.04**	**[1-3]**	**0.24**	

*assuming 6 courses of additional OIC treatment per year in the base case analysis.
95% confidence intervals (CI) were estimated based on the certainty scores provided by the experts from the panel during the second round. 1-certain, low risk of the figure being wrong (± 10% relative divergence possible); 2-reliable, some risk of being wrong (± 20%); 3-risky, substantial risk of being wrong (± 40%); or 4-unreliable, great risk of being wrong (more than 40%). Based on these results, average, lower and upper limit of resources used were calculated, and then multiplied with the unit cost of that item of resource use in order to obtain, respectively, the average, lower and upper limit of costs.

The most frequently reported complications of OIC reported in the Delphi-panel were fecal impaction, overflow diarrhea, anal fissures and hemorrhoids, resulting in drug costs, GP (home visits), tests and in-hospital procedures. The corresponding cost of

treating OIC complications in constipated patients was estimated at €318.90 or €36.80 per week (Table 3)[3].

The average cost of productivity loss was also estimated based on the Delphi panel outcomes. The Dutch GPs estimated that on average 23% range 17-29%] of the chronic pain patients who are receiving opioids are professionally active. Of these patients, on average 30% [range 22-38%] was unable to work due to constipation or due to complications of constipation. In these patients with prescribed sick leaves, there were on average 6.2 [range 4.6-7.8] working days absent per additional OIC treatment course. The hourly rate was estimated from the most recent manual of cost research (2010). In 2009, the average salary was €30.02 per hour, which was inflated to € 31.50 in 2014 based on the evolution of the prices of the collective labour agreement as per national guidelines ("Collectieve Arbeidsovereenkomst" (CAO), index varied from 125.4 in 2009 to 131.6 in 2013 –latest yearly value available at the time of the analysis). Assuming an average working day of 8 hours, the average cost of a working day loss was estimated at € 252.03. Combined with the Delphi panel data, the resulting indirect cost of OIC per patient was €107.32 per additional OIC treatment course (=252.0 x 0.23 x 0.30 x6.2). The corresponding cost of productivity losses caused by OIC in constipated patients was estimated at on average €107.32 [range 19-195] per additional OIC treatment course and on average €12.38 [range 2-23] per week (Table 3).

The direct costs not related to health care were estimated as the cost of transport from the patient's home to the hospital and back, including a parking cost. The 2009 unit costs per km with a personal car (€0.22/km) and the average parking cost (€3.36) were obtained from the 2010 costing manual values, inflated to 2014 using the Dutch CPI index. The transport cost for each treatment performed in the hospital (day clinic or in-hospital) was calculated as follows: (7km (as per national guidance) x €0.22) x 2 + €3.36 = €6.30. It was then multiplied with the proportion of patients requiring the treatment. The total transport costs remained marginal given the relative small proportion of patients going to the hospital for additional OIC treatment and treatment of OIC complications. The corresponding cost of transport related to additional OIC treatment and treatment of OIC complications in the hospital (day-care or in-hospital stay) or out-patient hospital visits was estimated at €2.04 per intervention and €0.24 per week (Table 3).

Inputs for health states

The treatment effect was modeled according to the analysis performed by Koopmans et al. [21,] for the laxative-refractory OIC population, which is a sub-group of patients in the OXN9001 trial. Patients were considered laxative-refractory when their BFI was above 28.8 despite the use of at least 2 laxatives of a different ATC level 4 class. A switch from opioids plus laxative treatment to PR OXN was associated with a reduction in the proportion of constipated patients over time[21]. The weekly rates of OIC are presented in Table

4. In the PR OXY arm, the baseline rate of constipated patients (91.4%; not all patients were constipated some patients did not tolerate the laxative treatment) was assumed unchanged until the end of the model horizon. The rational for the latter assumption was the absence of other treatments in this specific patient population treated with opioids and suffering from laxative-refractory OIC. The patients need a treatment with opioids and are unresponsive to laxatives. So in clinical practice these patients will be kept on an optimal laxative schedule and they will receive additional OIC treatment to temporarily relieve OIC when needed[19] (Table 4).

To allow modelling beyond 12 weeks, it was assumed that the BFI values achieved at the end of 12-week treatment period would remain constant for both treatment groups until the end of the model (52 weeks). This was a conservative assumption given long-term extension phase study results, showing sustained benefit of PR OXN relative to PR OXY over a 12-month period[42].

Table 4. Weekly proportions of OXN patients in "constipated" and "non-constipated" health states

Week	Non constipated (« normal BFI score »)	Constipated (BFI score >28.8)	95% CI
	n/N (%)	n/N (%)	
Week 0 (Day 1)	3/35 (8.6%)	32/35 (91.4%)	[82-100]
Week 1 (Day 8)	12/33 (36.4%)	21/33 (63.6%)	[47-80]
Week 2 (Day 15)	16/32 (50.0%)	16/32 (50.0%)	[33-67]
Week 4 (Day 29)	13/29 (44.8%)	16/29 (55.2%)	[37-73]
Week 8 (Day 57)	13/27 (48.1%)	14/27 (51.9%)	[33-71]
Week 12 (Day 85)	14/35 (40.0%)	21/35 (60.0%)	[44-76]

95% confidence intervals (CI) around each proportion p were estimated as follows: p +/- sqrt(p*(1-p)/N)

Quality of life inputs (utility values)

For laxative-refractory patients no utility values were available in the pooled analysis, since there were a limited number of non-constipated patients in the trial[21]. To obtain utilities specifically related to constipation status a literature search was performed which revealed three publications in which impact QoL was measured in relation to constipation in the Netherlands[2]. The article by Penning-van Beest was the only article describing the impact of OIC on QoL, using the EQ-5D score. In this publication the OIC-specific impact on QoL of patients treated with opioids for pain was measured in terms of disutility, applied to constipated vs. non-constipated patients with non-advanced disease[2]. The utility level was determined by the presence or absence of OIC. In a population with non-advanced disease (assumed to represent a non-malignant-pain population), the average EQ-5D utility was 0.65 [0.22-0.78] without OIC ($=U_{non\text{-}OIC}$) and 0.31 [0.17-0.73] with OIC (U_{OIC}), i.e. a disutility of 0.34 [0.32-0.36] due to OIC.

Deterministic sensitivity analyses

It was important to determine which inputs had the most significant impact on model results and whether particular inputs increased or decreased the ICER. The variations of a number of variables were tested separately and their impact on the ICER was presented in a Tornado diagram. Table 5 represents the variables that were tested separately including the range tested as well as the method used.

Table 5. Parameter limits used in the univariate sensitivity analysis

Model parameter	Mean Base case	Range (lower limit-upper limit	Source
Scenario 1, base case			
% of patients with OIC, OXN arm	cf Table 1	+/- 25%	Koopmans 2014, as per 95% confidence intervals
% of patients with OIC, OXY arm	Cf Table 1	+/- 25%	Koopmans 2014, as per 95% confidence intervals
N opioid mg/day, OXN	54.5mg	+/- 25%	Koopmans 2014
Model duration	52 wks	12 wks	Koopmans 2014 Blagden 2014
Treatment duration	100% of time	25-80%	Assumption
Utility constipated state	0.65	0.22-0.78	Penning van Beest 2010, as per published 95% CI
Disutility due to OIC	0.34	+/-25%	Penning van Beest 2010, as per 95% CI around the disutility
Cost of resources use (incl. complications), per week	€56.60	+/-33%	Delphi NL (updated 2014), as per certainty scores* (Table 7 and Table 10)
Cost of productivity loss caused by OIC, per week	€12.38	+/-80%	Delphi NL (updated 2014) as per certainty scores*

StdErr: standard error;

Probabilistic sensitivity analysis

The model conducted probabilistic sensitivity analysis (PSA) on the following major model inputs: utility values; probability of constipation over time; average oxycodone dose; unit costs of additional OIC treatment in constipated patients; cost of laxatives. A second order Monte-Carlo simulation i.e. probabilistic sensitivity analysis (PSA) was undertaken based on 3000 simulations.

Beta distributions were used for probabilities and disutility score, gamma distributions for costs, and normal distributions for other continuous variables (dosages, durations). The details on the distributions used in the PSA are presented in Table 6.

A cost-effectiveness plane representing the outcome of each simulation as a dot with QALYs gained with OXN vs. OXY on the x-axis and incremental costs on the y-axis and an acceptability curve showing the probability for OXN to be cost-effective compared to OXY depending on the willingness-to-pay (WTP) of the health care payer were derived

Table 6. Distribution and parameter limits used in the probabilistic sensitivity analysis

Model parameter	Mean	Distri. PSA	Distri. Param.
% of pts with OIC, OXY (week 0)	91.4%	Beta	718-68
% of pts with OIC, OXN, week 1	64%	Beta	20-12
% of pts with OIC, OXN, week 2	50%	Beta	16-16
% of pts with OIC, OXN, week 4	55%	Beta	15-13
% of pts with OIC, OXN, week 8	52%	Beta	13-13
% of pts with OIC, OXN, week >=12	60%	Beta	20-14
N opioid mg/day	54.5mg	Normal	54.5, 0.60
Laxative cost with OXY per day	€2.11	Gamma	1, 2.11
Laxative cost with OXN, per day	€0.09	Gamma	1, 0.24
Utility non constipated	0.65	Beta	7-4
Disutility due to OIC	0.34	Beta	531-1031
Costs additional OIC treatment,	€ 19.75	Gamma	1, 19.75
Costs of OIC complications cost,	€ 36.70	Gamma	1, 36.70
costs of OIC-related transport costs,	€ 0.24	Gamma	1, 0.24
Costs of OIC-related productivity loss	€ 12.38	Gamma	1, 12.38

from the PSA. To ease the interpretation of the PSA results a range of WTP thresholds was used: from 20,000 €/QALY, which is the threshold mentioned in The Netherlands for diseases with a low burden of disease to 50,000 €/QALY, as can be encountered when the burden of disease is higher.

Scenario analyses

Besides deterministic and probabilistic sensitivity analyses also a set of different scenarios were analyzed, based on feedback from real-life studies[43,44]. First scenario a scenario in which 3 OIC interventions per year were assumed based on low value obtained in the Delphi panel (base case 6 interventions). Other scenario's involved excluding costs of constipation-related complications and excluding indirect costs. A last scenario involved a scenario in which costs were derived from Dik et al. 2014[44] who investigated constipation-related direct medical costs in 16 887 patients newly diagnosed with chronic constipation in the Netherlands.

RESULTS

Base case

Table 7 shows the base case results. Patients treated with PR OXN had higher analgesia costs (€2,032) compared to PR OXY. Compared to OXY, patients treated with PR OXN

had lower laxative treatment costs, lower additional OIC treatment costs and lower OIC complication costs as well as lower costs for OIC-related productivity loss and lower OIC-related transport costs (total savings amounted to €1269 over 52 weeks). The incremental cost of PR OXN versus PR OXY was € 762.90 over 52 weeks. Relative to PR OXY, PR OXN gave an incremental QALY gain of 0.1102. Resulting in an ICER of € 6,924 per QALY gained. This value is deemed cost-effective, assuming a willingness-to-pay threshold of €20,000 per QALY gained.

Table 7: Incremental and total costs in the base case analysis

Cost item	OXN	OXY	Incremental OXN vs. OXY
Opioid costs (pain therapy)	€ 2,427.88	€ 396.24	€ 2,031.64
Laxative treatment costs (concomitant to opioid)	€ 4.92	€ 109.77	-€ 104.84
Additional OIC treatment costs	€ 606.00	€ 938.88	-€ 332.88
OIC complications costs	€ 1,125.71	€ 1,744.07	-€ 618.36
OIC-related transport costs for in-hospital additional OIC treatment and treatment of OIC complications	€ 7.36	€ 11.41	-€ 4.04
OIC-related costs for productivity losses	€ 379.78	€ 588.40	-€ 208.62
Total cost (Societal)	**€ 4,551.66**	**€ 3,788.75**	**€ 762.90**
QALY	**0.4494**	**0.3392**	**0.1102**

Results are undiscounted (time horizon < 1 year).
ICER base case analysis (societal perspective):€6,924, ICER base case analysis (without societal costs):€8,853

Univariate (deterministic) sensitivity analyses

The results of the univariate sensitivity analysis testing relative variations around the base case values as described in table 5 are presented in the Tornado diagram in Figure 2.

The utility level of the "non-constipated" patients resulted in an ICER variation changing the value to PR OXN dominated (lower costs and more QALYs gained relative to PR OXY) and € 5,009 per QALY gained when the utility in the "non-constipated" health state was changed to from 0.22 and 0.78, respectively (base case = 0.65). Increasing the utility level of non-constipated patients results in a lower ICER.

The variations of -25% to +25% around the base case OIC rate of the weekly proportions of patients with OIC in the PR OXN arm resulted in a higher ICER to €1,470 and 21,284 per QALY gained. As expected the proportion of patients with OIC in the PR OXN arm has an impact on the ICER.

Varying the mean daily dose of opioid received in the PR OXN and PR OXY arms, with variations from 41 to 68mg/day resulted in an ICER change to € 2,318 and 11,535 QALY gained. However, the average dispensed daily dose of PR OXY per patient has been stable during the years 2009-2013 at approximately 35 mg per day (www.gipdatabank.

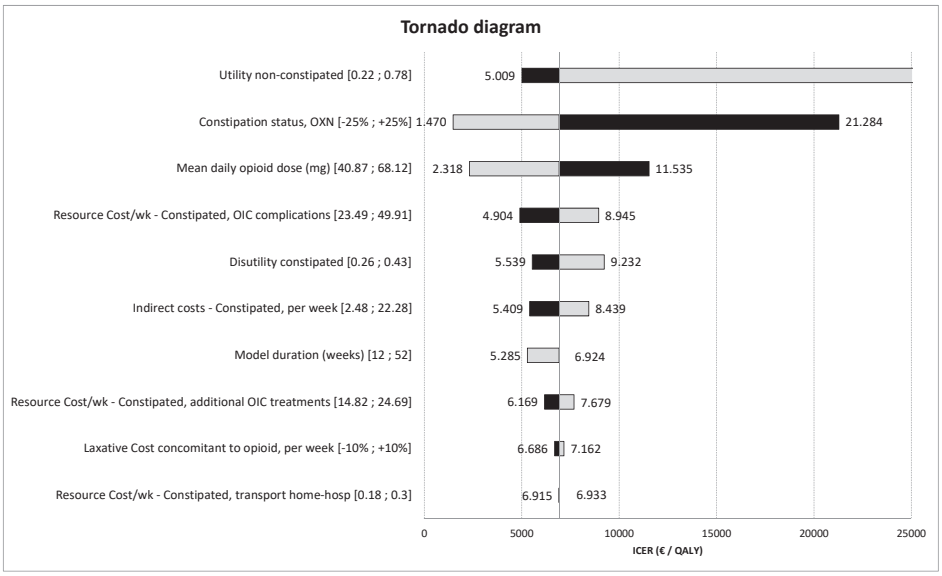

Figure 2: Tornado diagram, ICER of OXN vs. OXY, societal perspective (univariate sensitivity analysis). In blue: ICER obtained with the low value of the parameter; in red: ICER with the high value parameter. ICER base case analysis: €6,924 per QALY gained.

nl). An increase to an average daily dose of 68 mg is not expected as PR OXN results in comparable pain relief compared to PR OXY. When costs of OIC complications or costs of additional OIC treatment course are varied from -36% to +36% around the base case value, ICER changed to €8,945 and €4,904 per QALY gained. Varying the disutility associated with the "constipated" state to 0.26 and 0.43 results in a change in ICER to € 9,232 and € 5,539 per QALY gained. The ICER increases when the impact of OIC on patients' QoL increases. When the mean indirect costs (costs of OIC-related productivity losses) are varied from -80% to +80% around the base case value during additional OIC treatment courses the ICER changes to €8,439 and €5,409 per QALY gained.

Probabilistic sensitivity analysis

The PSA outcomes are described in Table 8.

On average over 3000 simulations, the mean (SD) QALYs gained with PR OXN vs. PR OXY were 0.11 (0.022) and the mean (SD) incremental costs were € 765 (822) per patient, resulting in an ICER of €6,953 per QALY gained. This result is in line with the base case deterministic conclusion. The cost-effectiveness plane (scatter plot) is shown in Figure 3.

Each dot represents the outcome of a simulation. There were 15% in the South-East quadrant (lower costs, higher QALYs i.e. dominant situation of PR OXN vs. PR OXY).At a threshold of €20,000 per QALY gained a total of 96% simulations are cost-effective and

100% at a €50,000 per QALY gained threshold. The acceptability curve is shown in Figure 4 and confirms the findings above.

Table 8: PSA outcomes OXN vs. OXY, 3000 simulations

Strategy	Mean (SD) Cost	Mean (SD) ΔCosts	Mean (SD) QALYs	Mean (SD) ΔQALYs
OXY (ref)	3,754.4 (2,112.6)		0.343 (0.116)	
OXN	4,519.2 (1,371.9)	764.8 (821.6)	0.453 (0.118)	0.11 (0.022)

ΔCosts: difference in cost per patient treated with OXN vs. OXY
ΔQALYs: difference in QALYs gained per patient treated with OXN vs. OXY
SD: standard deviation.

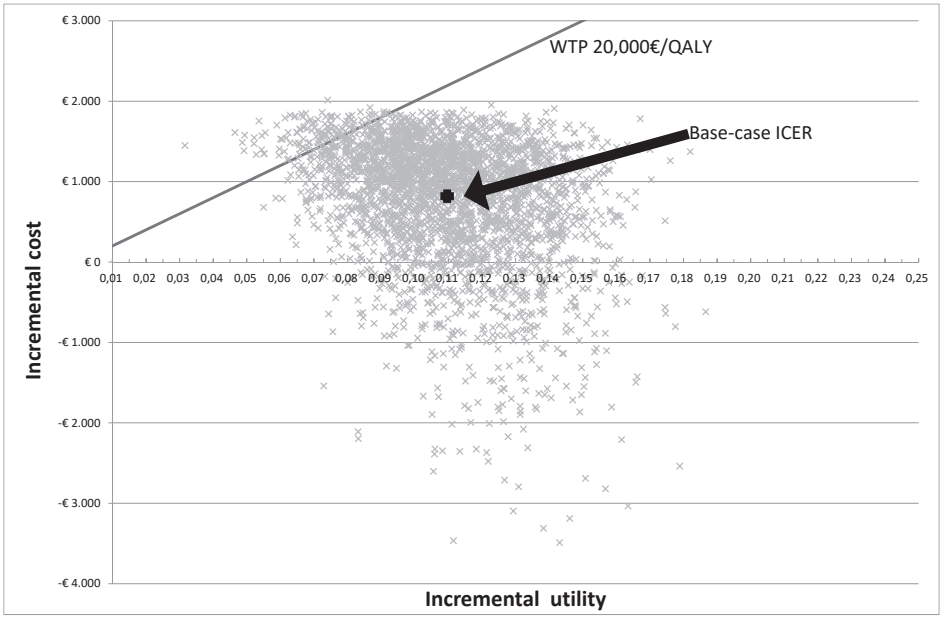

Figure 3: Cost-effectiveness plane.

Other scenario analyses

Scenario assuming 3 additional OIC treatment courses per year (base case 6 courses per year)
This scenario demonstrates that decreasing the number of additional OIC treatment courses results in an increase of the ICER to €11,241 per QALY gained.

Scenario excluding indirect costs (OIC-related productivity costs)
This scenario shows that there is an impact of OIC-related productivity loss on the ICER. As expected exclusion of these costs led to a higher ICER of €8,818 per QALY gained.

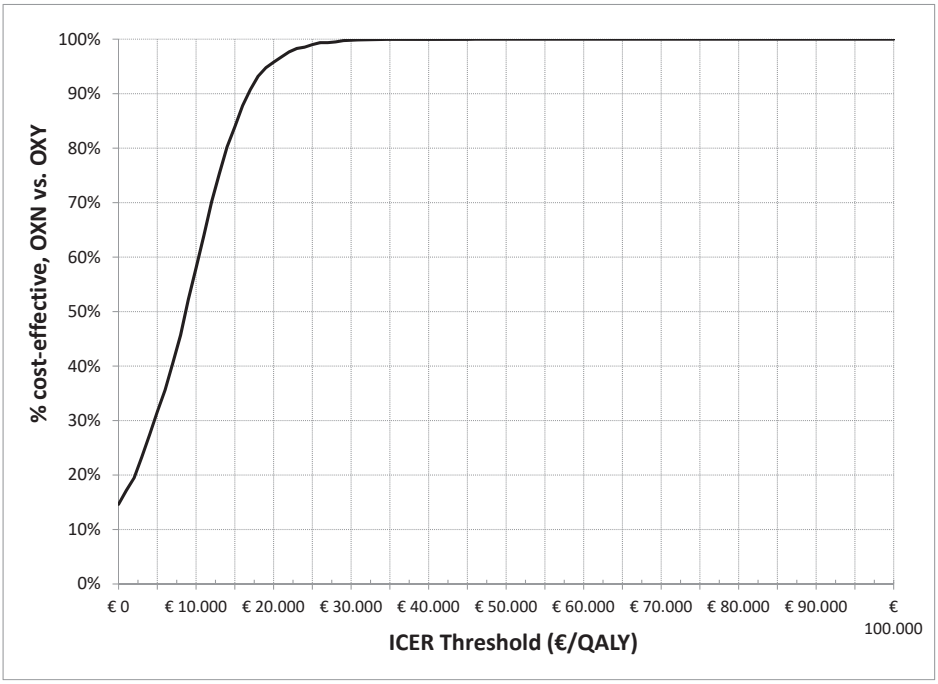

Figure 4: Acceptability curve PR OXN vs. PR OXY, PSA

Scenario excluding costs OIC complications

As expected costs of OIC complications have an impact on the ICER increasing it to €12,536.

Scenario using Chronic constipation related costs from Dutch Health Insurance Claims database (Dik et al.).

When using chronic constipation related costs in patients with persistent constipation from the Dutch health care insurance claims database the ICER increases to €14,761. In this publication all costs in the claims database related to chronic constipation were included from secondary care.

The results of the base case analysis, deterministic and probabilistic sensitivity analyses as well as the scenario analyses are depicted in table 9.

Table 9: Results of univariate sensitivity & scenario analyses

Subject	**Δcosts**		**ΔQALYs**			**ICER (€/QALY)**
Base case	**762.9**		**0.1102**			**6,924**
univariate sensitivity analyses	LOW			HIGH		
	Δcosts	**ΔQALYs**	**ICER (€/QALY)**	**Δcosts**	**ΔQALYs**	**ICER (€/QALY)**
Model duration (weeks) [12 ; 52]	148.3	0.028	5,285	762.9	0.110	6,924
Mean daily opioid dose (mg) [40.875 ; 68.125]	255.4	0.110	2,318	1270.9	0.110	11,535
Resource Cost/wk - Constipated, additional OIC treatments [14.82 ; 24.69]	846.1	0.110	7,679	679.7	0.110	6,169
Resource Cost/wk - Constipated, OIC complications [23.49 ; 49.91]	985.5	0.110	8,945	540.3	0.110	4,904
Resource Cost/wk - Constipated, transport home-hosp [0.18 ; 0.3]	763.9	0.110	6,933	761.9	0.110	6,915
Laxative Cost concomitant to opioid, per week [-10% ; +10%]	789.1	0.110	7,162	736.7	0.110	6,686
Indirect costs - Constipated, per week [2.476 ; 22.284]	929.8	0.110	8,439	596.0	0.110	5,409
Disutility constipated [0.255 ; 0.425]	762.9	0.083	9,232	762.9	0.138	5,539
Utility non-constipated [0.221 ; 0.78]	762.9	-0.029	OXN Dominated	762.9	0.152	5,009
Constipation status, OXN [-25% ; +25%]	235.4	0.160	1,470	1287.7	0.061	21,284
	Δcosts		**ΔQALYs**			**ICER (€/QALY)**
Scenario analyses						
3 additional OIC treatment courses/year	1,238.5		0.1102			11,241
Excluding OIC indirect costs (OIC-related productivity loss)	971.5		0.1102			8,818
Excluding costs of OIC complications	1,381.2		0.1102			12,536
Costs from Health insurance claims database (secondary care, Dik 2014)	1,626.34		0.1102			14,761

DISCUSSION

PR OXN combines the strong opioid receptor agonist oxycodone and the opioid receptor antagonist naloxone. PR OXN has proven equivalent analgesic efficacy to PR OXY with significant improvements in bowel function in chronic non-malignant pain[30-35] as well as in moderate/severe malignant pain[36,37]. It is important to assess cost utility of PR OXN treatment for laxative-refractory patients, as treatment with PR OXN is more expensive than treatment with PR OXY.

This cost-utility analysis demonstrates that treatment with PR OXN generates an ICER well below the commonly applied thresholds in the Netherlands. The ICER is similar

to that generated in a previous cost-utility model of PR OXN compared with PR OXY[1]. Under a conservative approach taking into account the optimal laxative schedule and assuming a continuous opioid treatment, it demonstrated cost-effectiveness of PR OXN plus rescue bisacodyl for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC compared to OXY plus a laxative regime with an ICER of €6,924 per QALY gained.

Several sensitivity and scenario analyses show the robustness of the model (ICERs between €1,470 and €21,284 per QALY gained; the latter in patient who are unresponsive to treatment with PR OXN). The probability of being cost-effective for PR OXN vs. PR OXY was 96% and 100% at a WTP threshold of €20,000 to €50,000 per QALY gained, respectively.

The univariate sensitivity analysis in which the proportion of constipated patients in the OXN-arm was increased with 25% resulted in the highest ICER €21,284 per QALY gained. In general, it can be discussed that patients with OIC unresponsive to treatment with PR OXN most probably suffer from constipation caused by other factors than constipation . For these patients other more invasive pain management methods could be explored in real-life.

A scenario analyzing the impact of decreasing the number of additional OIC courses per year from 6 to 3 resulted in increase of the ICER to €11,241 per QALY gained. However, in this specific patient population patients on opioids who are suffering from laxative-refractory OIC it is not expected that the number of additional OIC treatment courses will decrease. Actually in the Delphi panel it was shown that in this specific patient population the number might increase to 1 additional OIC treatment course every month i.e. 12 per year, implying a conservative base case.

Also a scenario was analyzed in which the costs of complications were excluded. This is in line with the pharmaco-economic report of subcutaneous (sc) methylnaltrexone that was submitted to obtain reimbursement in the Netherlands, in which also no costs for complications were added[45]. As expected costs of OIC complications have an impact on the ICER increasing it to €12,536 per QALY gained. However, this ICER is still lower than the national threshold of €20,000 per QALY gained. In comparison the ICER obtained with sc methylnaltrexone was €33,464 per QALY gained. Both patient populations consisted of laxative refractory OIC patients. Difference between the population is the palliative care setting for sc methylnaltrexone compared with the non-malignant patients in our analysis.

Finally, a scenario was analyzed using chronic constipation related costs in patients with persistent constipation from the Dutch health care insurance claims database. In this scenario the ICER increased to €14,761[42]. However, according to the authors of the publication there might be an underestimation of costs as laxatives and treatments for constipation might also have been prescribed as part of the treatment for the underly-

ing disease. In those cases, diagnostic related groups (DRGs) for chronic constipation might not be claimed, leading to an underestimation of the actual chronic constipation related direct medical costs. Also GP-related care (primary care) was not included in the costs. According to the Delphi panel a substantial proportion of costs of additional OIC management OIC complications originated from GP-care (primary care).

In current guidelines a laxative regime is advised for the prevention and treatment of OIC[19,41]. Despite the use of this laxative regime, a group of patients will suffer from laxative-refractory OIC[19,41]. Recently, for these patients besides PR OXN, subcutaneous (sc) methylnaltrexone and naloxegol have also become available in the Netherlands for non-malignant pain patients. These options have not been taken into account in this model. However, medication costs of PR OXN are the lowest with current list-prices of these medications; sc methylnaltrexone approximately €178,- per week (assuming 4 flacons with 0.6 ml 20 mg/ml methylnaltrexone per week), naloxegol approximately €36,75 per week (assuming 1 tablet of 25 mg per day) and PR OXN approximately €16,13 per week (assuming 14 tablets of 10 mg per week) and assuming a comparable clinical benefit of PR OXN, sc methylnaltrexone and naloxegol on OIC, (source: www.medicijnkosten.nl; last accessed: april 29th 2018). However, until now there are no data available that compare the clinical benefit between the different peripherally acting mu-opioid receptor antagonists (PAMORA's) and the comparability found in systematic reviews still needs to be confirmed. Moreover, also side effects and ease of administration should be taken into account in establishing the clinical benefit from a societal perspective.

No utility values were available in the pooled analysis for this specific sub-population of patients, since there were a limited number of non-constipated patients in the trial[21] There is no doubt that constipation contributes to the QoL in chronic pain patients[1,2]. In this economic evaluation the utility level corresponding to the health states "constipated" and "non-constipated" in a Dutch population treated with opioids for pain caused by a non-advanced disease was taken from the article by Penning-van Beest et al. (2010)[2]. These utilities were also used in the economic evaluation of sc methylnaltrexone[45]. Moreover, several observational studies in the real-world treatment setting support improvements in quality of life for patients with chronic pain receiving PR OXN[43,46-49].

Limitations

The main limitations of the analysis are pertaining to: (1) the economic data inputs, which were obtained from a Delphi panel of 12 Dutch GPs so that the outcomes are based on the perceptions of primary care physicians. As indicated in Dunlop et al. 2012, other groups of healthcare professionals, like nurses and secondary care specialists treating constipation, may report different resource use and costs[1]. To address this problem also a scenario analysis was performed and discussed using the costs in secondary care from the Dutch Health Insurance Claims Database as described by Dik et al. 2014[44].;

(2) Model and cost inputs were from 2015. Since 2015 drug prices might have changed as also generic macrogol plus electrolytes has entered the market. Moreover, also costs of PR OXN have dropped whereas costs for PR OXY have not dropped further. However, costs for additional OIC treatments and costs of treating OIC complications had a far greater impact on the cost-difference than laxative costs. Besides generic entry also other PAMORA's like sc methylnaltrexone, oral naloxegol and naldemedine will and/or have become available to patients with laxative-refractory OIC which could impact the model. As described above PR OXN seems to be a cheaper treatment option than sc methylnaltrexone and naloxegol for patients using oxycodone, but the impact of all PAMORA's on cost-utility of OIC treatments from a societal perspective remains to be elucidated; (3) a possible lack of power of the Penning-van Beest study[2] providing the utility scores and disutility. Although the difference in utility level between OIC and non-OIC patients was significant in the non-advanced disease population ($p<0.01$) the confidence intervals around the utility scores were wide. This is reflected by the univariate sensitivity analysis which showed the sensitivity of the model to the utility level of non-OIC patients; (4) the rate of OIC was based on trial data until week 12 and extrapolated based on extension trial data until week 52. A potential area for future research is to develop parametric survival curves to more accurately estimate the treatment benefits beyond 12 weeks; (5) constipation status was based on relatively low patient numbers in the analysis. However, real-life observational studies in larger patient populations suggest similar response rates[43,49]. (6) finally, the health states were based on constipation, the most common side-effect of opioid treatment. However, PR OXN may counteract other aspects of opioid-induced bowel disorders (such as abdominal pain, cramping and bloating) that may require additional healthcare resources. It is therefore possible that a model examining these aspects on top of OIC may show a greater incremental QALY gain from PR OXN compared with OXY[1].

Appropriateness comparator

In order to have an appropriate comparison the model should reflect treatment in real-life practice. In this model PR OXN was compared to its opioid component PR OXY, as the addition of naloxone does not affect pain relief of oxycodone nor the safety-profile (with the exception of constipation). Furthermore oxycodone is the most prescribed oral strong opioid in the Netherlands[50]. In current guidelines a laxative regime is advised for the prevention and treatment of OIC[19,41]. Therefore patients in the PR OXY-arm received laxative therapy on top of their opioid treatment and for patients with PR OXN as needed bisacodyl was used in the model, as was the case in the clinical trials. Other peripherally acting mu-opioid receptor antagonists like sc methylnaltrexone and naloxegol, were not used as a comparator since at time of model preparation they were not licensed in the Netherlands for the treatment of OIC in non-malignant pain patients.

CONCLUSIONS

The present pharmaco-economic study is based on available evidence in non-malignant pain patients treated with opioids and suffering from laxative-refractory OIC, using pivotal trial data. It demonstrated cost-effectiveness of PR OXN for opioid-treated patients with non-malignant pain suffering from laxative-refractory OIC with an ICER of € 6,924 per QALY gained. Several sensitivity and scenario analyses show the robustness of the model. The overall conclusion is that PR OXN has a probability of being cost-effective compared to PR OXY of 96% and 100% at WTP thresholds of respectively € 20,000 to €50,000 per QALY.

TRANSPARENCY

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This study was designed by Mundipharma Pharmaceuticals BV There is no financial interest linked to the preparation, scientific advice and authorship of the article for the authors. No grants, equipment or drugs were supplied by the sponsor. F.J.P.M. Huygen and M. Dirckx provided scientific advice to Mundipharma Pharmaceuticals BV. All authors were involved in the development, writing, critical reviewing and approval of this manuscript.

Declaration of financial/other relationships

M. Dirckx and F.J.P.M. Huygen have nothing to disclose.

Y.J.B. van Megen, and G. Koopmans-Klein report personal fees from Mundipharma Pharmaceuticals BV, during the conduct of the study and personal fees from Mundipharma Pharmaceuticals BV, outside the submitted work. W. Dunlop reports personal fees from Mundipharma International at time of study conduct and article drafting and personal fees from Mundipharma International outside the submitted work.

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