HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 September 2012

The Opinion of the Transparency Committee of 20 June 2012
was examined at a hearing on 19 September 2012

Examination of the dossier for proprietary medicinal products included for a 5-year period starting on 31 March 2007 (Official Gazette of 23 December 2008)

OXYCONTIN PR 5 mg, prolonged-release tablet
B/28 (CIP code: 366 903-4)

OXYCONTIN PR 10 mg, prolonged-release tablet
B/28 (CIP code: 354 209-0)

OXYCONTIN PR 20 mg, prolonged-release tablet
B/28 (CIP code: 354 215-0)

OXYCONTIN PR 40 mg, prolonged-release tablet
B/28 (CIP code: 354 222-7)

OXYCONTIN PR 80 mg, prolonged-release tablet
B/28 (CIP code: 354 294-8)

OXYNORM 5 mg, hard capsule
B/14 (CIP code: 362 419-0)

OXYNORM 10 mg, hard capsule
B/14 (CIP code: 362 421-5)

OXYNORM 20 mg, hard capsule
B/14 (CIP code: 362 423-8)

Applicant: MUNDIPHARMA

Oxycodone hydrochloride
ATC code: N02AA05
Narcotic – Prescription limited to 28 days.

Date of Marketing Authorisations (national procedure)

OXYCONTIN PR 10, 20, 40 and 80 mg: 5 December 2000
OXYCONTIN PR 5 mg: 14 March 2005
OXYCONTIN PR 15, 30, 60 and 120 mg: 11 March 2008
OXYNORM 5, 10, 20 mg hard capsule: 11 June 2003
OXYNORMORO 5, 10 mg: 19 July 2007
OXYNORMORO 20 mg: 16 July 2007

Date of latest revision of Marketing Authorisation: 9 July 2010 (amendments to the wording of the indication)

Joint renewal of the following medicinal products:

OXYCONTIN PR 15 mg, prolonged-release tablet
B/28 (CIP code: 384 584-4)

OXYCONTIN PR 30 mg, prolonged-release tablet
B/28 (CIP code: 384 587-3)

OXYCONTIN PR 60 mg, prolonged-release tablet
B/28 (CIP code: 384 598-5)

OXYCONTIN PR 120 mg, prolonged release tablet
B/28 (CIP code: 384 602-2)

OXYNORMORO 5 mg, orodispersible tablet
B/14 (CIP code: 380 421-3)

OXYNORMORO 10 mg, orodispersible tablet
B/14 (CIP code: 380 425-9)

OXYNORMORO 20 mg, orodispersible tablet
B/14 (CIP code: 380 428-8)

Reasons for request:

- Renewal of inclusion on the list of medicines refundable by National Health Insurance of the medicinal products listed below,
- Extension of the indication for non-cancer related pain for all forms OXYCONTIN PR, OXYNORM and OXYNORMORO including those included for hospital use only, in particular:

OXYNORM 10 mg/ml, oral solution
One 30 ml vial with a graduated syringe for oral administration
(CIP code: 366 912-3)

OXYNORM 10 mg/ml, solution for injection
B/5 ampoules of 1 ml (CIP code: 366 914-6)
B/5 ampoules of 2 ml (CIP code: 366 915-2)
B/4 ampoules of 20 ml (CIP code: 392 317-1)

OXYNORM 50 mg/ml, solution for injection
B/5 ampoules of 1 ml (CIP code: 387 625-3)

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Oxycodone hydrochloride

1.2. Indication

Previous wording:

"OXYNORM and OXYNORMORO
For the treatment of cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years).

OXYCONTIN PR
For the treatment of chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)."

New wording forming the subject of the application (**concerning all forms)**:
"**For the treatment of severe pain** which can be adequately managed only with strong opioid analgesics, in particular cancer pain.

1.3. Dosage

"Oral forms

For adult use only
As with all analgesic medicines, the dose should be adjusted to the pain intensity, the quantity of analgesic taken previously and to the clinical response of each patient.

Initial dose

Patients receiving strong opioids for the first time

OxyContin PR: Use the dose of 10 mg every 12 hours.

OxyNorm – OxyNormORO: Use the dose of 5 mg every 4-6 hours.

Patients previously treated with strong opioids

The initial dose is determined based on the equivalent daily dose of morphine taken previously. As an indication, and in the absence of a clearly established equivalent, the equianalgesic ratio is: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. The dose of oxycodone will be approximately half the previous dose of morphine administered.

Patients with mild to moderate hepatic impairment, renal impairment, elderly patients or weak patients

Oxycodone must be administered with care. Start treatment at the lowest dose, 5 mg every 12 hours for prolonged-release tablets, 5 mg every 4 to 6 hours for hard tablets and orodispersible tablets, 2.5 mg every 6 hours for the oral solution, so as to minimise the incidence of adverse effects. The dose is then adjusted individually, based on the clinical response of the patient.

Dosage adjustments

A change in dose is justified when previously prescribed doses are no longer effective.

Evaluation frequency

Patients should not remain on a dose that appears to be ineffective. The patient must be closely monitored so that the dose is sufficient to correctly control the pain. In practice, a daily evaluation is recommended at the start of treatment.

Dosage increases

If the pain is not controlled with prolonged-release tablets, the dose can be increased in 25 to 50% increments, while maintaining the dose interval of 12 hours.

If pain is not controlled with immediate release forms, the dose may be increase in 25% to 50% increments:

- either by reducing the interval between medication being taken (if the pain is controlled at the start , but not at the end of the time period),
- or by increasing the dose each time the medication is taken (if the pain is not controlled at any time between the two doses).

While making these dose adjustments, there is no upper dose limit as long as adverse effects are also controlled.

Changing pharmaceutical form

When changing from the immediate release form to prolonged-release tablets, the daily dosage should remain unchanged.

Discontinuation of treatment

It may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Injectable forms

For adult use only

The relationship between the dose, efficacy and safety of the product varies from patient to patient. It is therefore very important to frequently evaluate the efficacy and safety, making necessary changes progressively based on the needs of the patient (see dose adjustments). There is no maximum dose, as long as the adverse effects are being controlled.

As an indication, the order of equivalence for doses based on the method of administration is:

Oral use	SC	IV
1 mg	0.5 mg	0.5 mg

The simultaneous taking of oxycodone via two different administration methods is to be avoided as there is a risk of overdose due to the different kinetic properties of the oral and injectable forms.

Methods of administration

Intravenous injection or intravenous infusion,

Sub-cutaneous injection or sub-cutaneous infusion.

Initial dosage

The dosage depends on the intensity of the pain, the general health of the patient and previous and concomitant treatments.

Treatment of chronic cancer-related pain

IV and sub-cutaneous routes

For patients receiving strong opioids for the first time

The initial dose is 0.125 mg/kg/day (approximately 7.5 mg/day), with continuous infusion being preferred over repeated injections every four to six hours.

For patients already receiving oxycodone orally

The initial dose is calculated based on the following ratio: 2 mg oral oxycodone is equivalent to 1 mg injectable oxycodone. This ratio is an indication only, and inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

For patients who have pain that varies in intensity throughout the day

It is possible to use a patient-controlled analgesia system; the continuous infusion at the normal dosage is combined with a self-administrated bolus, with a dose equivalent to about one hour of infusion, followed by a minimum period of five minutes where injection is not possible (refractory period).

As an indication, the equianalgesic ratio of injectable oxycodone and injectable morphine is on average 1:1. This ratio is an indication only, and inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Patients with non-severe hepatic impairment, renal impairment, elderly patients or weak patients

Oxycodone must be administered with care. Treatment should be started at the lowest dose possible. The dose is then adjusted individually, based on the clinical response of the patient.

Dosage adjustments

A change in dose is justified when previously prescribed doses are no longer effective.

Discontinuation of treatment

It is appropriate to taper the dose gradually to prevent symptoms of withdrawal."

2 REMINDER OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

This reminder only concerns the proprietary medicinal products that are the subject of the renewal of inclusion on the list of medicines refundable by National Health Insurance (OXYCONTIN PR, OXYNORM hard capsules and OXYNORMORO).

- OXYCONTIN PR prolonged-release tablets

Opinion of 20 June 2001 – Initial inclusion 10 mg, 20 mg, 40 mg, 80 mg:
The actual benefit of these proprietary medicinal products is substantial.
OXYCONTIN PR, prolonged-release tablet does not provide an improvement in actual benefit compared with other morphine based prolonged-release tablets.

Opinion of 7 September 2005 – Initial inclusion 5 mg:
The actual benefit of this proprietary medicinal product is substantial.
OXYCONTIN PR 5 mg does not provide an improvement in actual benefit compared with OXYCONTIN PR 10 mg, 20 mg, 40 mg and 80 mg.

Opinion of 3 January 2007 – Renewal of inclusion 5 mg, 10 mg, 20 mg, 40 mg, 80 mg:
The actual benefit of these proprietary medicinal products remains substantial in the Marketing Authorisation indications.

Opinion of 3 September 2008 – initial inclusion 15 mg, 30 mg, 60 mg, 120 mg :
The actual benefit of these proprietary medicinal products is substantial.
The new doses of OXYCONTIN PR do not provide an improvement in actual benefit (IAB V) compared with other pre-existing doses.

- OXYNORM hard capsule

Opinion of 26 November 2003 – Initial inclusion 5 mg, 10 mg, 20 mg:
The actual benefit of these proprietary medicinal products is substantial.
OxyNorm does not provide an improvement in actual benefit (IAB V) compared with OXYCONTIN PR. The Committee regrets the absence of a comparison of OXYNORM with an immediate release morphine sulphate.

Opinion of 3 January 2007 – Renewal of inclusion 5 mg, 10 mg, 20 mg:
The actual benefit of these proprietary medicinal products remains substantial in the Marketing Authorisation indications.

- OXYNORMORO orodispersible tablets

Opinion of 6 February 2008 – Initial inclusion 5 mg, 10 mg, 20 mg:
The actual benefit of these proprietary medicinal products is substantial.
These proprietary medicinal products are additions to the range and do not provide an improvement in actual benefit.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2012)

N : Nervous system
N02 : Analgesics
N02A : Opioids
N02AA : Natural opium alkaloids
N02AA05 : Oxycodone

3.2. Relevant comparator medicines

These are other strong opioids (WHO step III) included on the list of reimbursable and commercialised proprietary medicinal products:

- Morphine based administered orally and prolonged-release (comparable to OXYCONTIN PR)

Proprietary medicinal product	Indication	Latest Committee opinion
morphine sulfate		
SKENAN PR PR microgranules in hard capsule: 10, 30, 60, 100 and 200 mg	Persistent intense pain or pain unresponsive to other analgesics, especially cancer-related pain.	IR 10 February 2010: Substantial AB
MOSCONTIN Coated tablet: 10, 30, 60 and 100 mg MOSCONTIN PR PR film-coated tablet: 200 mg	Persistent intense pain or pain unresponsive to weaker analgesics, especially cancer-related pain.	IR 27 April 2011 Substantial AB
ZOMORPH PR 20, 40, 60, 120 and 200 mg, prolonged-release tablet	Severe, chronic and constant pain. This medicinal product is not appropriate for initial treatment; consequently its use is limited to patients whose pain is already being controlled with immediate release morphine or prolonged release morphine, taken twice daily.	Substantial AB (not commercialised)

IR: inclusion renewed, AB: Actual Benefit

- Morphine based administered orally and immediate release (comparable to OXYNORM, OXYNORMORO)

Proprietary medicinal product	Indication	TC opinion
morphine sulfate		
ACTISKENAN Hard capsule: 5, 10, 20 and 30mg	Intense pain or pain unresponsive to weaker analgesics, especially cancer-related pain.	IR 10 February 2010 Substantial AB
SEVREDOL Scored, film-coated tablet: 10 and 20 mg	Intense pain or pain unresponsive to weaker analgesics, especially cancer-related pain.	IR 27 April 2011 Substantial AB
ORAMORPH Oral solution: 10, 30 and 100 mg/5 ml, 20 mg/ml	Intense pain or pain unresponsive to weaker analgesics, especially cancer-related pain.	IR 1st December 2010 Substantial AB

- Morphine based administered via injection (comparable to OXYNORM solution for injection)

Proprietary product	Indication	TC opinion
morphine sulfate		
MORPHINE LAVOISIER Solution for injection in ampoules: 1 mg/ml 50 mg/ml	1 mg/ml **Intense pain and/or unresponsive to weaker analgesics**. 50 mg/ml Intense pain and/or unresponsive to weaker analgesics, before being treated with continuous administration of morphine via programmable medical devices.	IR 10 February 2010 Substantial AB
MORPHINE AGUETTANT Solution for injection in ampoules: 0.1, 1, 10, 20 and 40 mg/ml	0.1, 1, 10, 20 mg/ml Intense pain and/or unresponsive to weaker analgesics. 40 mg/ml Intense pain and/or unresponsive to weaker analgesics, before being treated with continuous administration of morphine via programmable medical devices.	Substantial AB
Morphine hydrochloride		
MORPHINE LAVOISIER Solution for injection in ampoule: 10 mg/ml 20 mg/ml	10 and 20 mg/ml Intense pain and/or unresponsive to weaker analgesics.	Substantial AB
MORPHINE RENAUDIN Solution for injection in ampoule: 1 mg/ml, 10 mg/ml, 20 mg/ml and 40 mg/ml	1, 10, 20 mg/ml Intense pain and/or unresponsive to weaker analgesics. 40 mg/ml Intense pain and/or unresponsive to weaker analgesics, before being treated with continuous administration of morphine via programmable medical devices.	Substantial AB

Other strong immediate- or prolonged-release opioids

Fentanyl		
DUROGESIC Transdermal patch: 12, 25, 50, 75 and 100 µg/**h**	Treatment of chronic severe pain, which can be adequately managed only by opioid analgesics. **(extension of the indication for non-cancer related pain in March 2008)**	10 December 2008 Cancer-related pain: Substantial AB; IAB: benefit retained non-cancer related pain : Insufficient AB
MATRIFEN (medicinal product essentially similar to DUROGESIC), transdermal patch 12 µg/hour, 25 µg/hour, 50 µg/hour, 75 µg/hour, 100 µg/hour	"Transdermal treatment of intense chronic pain, in combination with strong opioids, after their efficacy has been established."	Idem DUROGESIC
Buprenorphine TEMGESIC 0.2 mg, sublingual tablet	Intense pain, especially post-operative and neoplastic pain	18 October 2006 Substantial AB
Hydromorphone hydrochloride		
SOPHIDONE PR, PR hard capsule 4, 8, 16 and 24 mg	Treatment of intense cancer-related pain in cases of resistance or intolerance to strong opioids.	IR 4 July 2007 Substantial AB

Pethidine PETHIDINE RENAUDIN 50 mg/ml	Intense pain and/or unresponsive to weaker analgesics	18 January 2012 Low AB
Nalbuphine NALBUPHINE AGUETTANT 20 mg/ 2 ml NALBUPHINE MYLAN 20 mg/ 2 ml NALBUPHINE QUALIMED 20 mg/ 2 ml NALBUPHINE SERB 20 mg/ 2 ml	Intense pain and/or unresponsive to weaker analgesics.	Substantial AB

The equianalgesic ratio is 2:1 between oral morphine and oral oxycodone (2 mg of morphine = 1 mg of oxycodone) and 4:1 between oral oxycodone and hydromorphone (4 mg of oxycodone = 1 mg of hydromorphone) (see table below):

Conversion to equivalent oral morphine

INN	Ratio	Equivalent to the dose of oral morphine
Codeine	1/6	60 mg of C = 10 mg of morphine
Dihydrocodeine	1/3	60 mg of DC = 20 mg of morphine
Tramadol	1/5	50 to 60 mg of T = 10 mg of morphine
Pethidine	1/5 to 1/6	50 mg of P = 10 mg of morphine
IV Morphine	3	1 mg of IV morphine = 3 mg of oral morphine
SC or IM Morphine	2	1 mg of SC morphine = 2 mg of oral morphine
Oral Oxycodone	2	5 mg of O = 10 mg of oral morphine
Hydromorphone	7.5	4 mg of Hydromorphone = 30 mg of morphine
Buprenorphine SL	30	0.2 mg of B = 6 mg of oral morphine
Nalbuphine SC	2	5 mg of Nalbuphine SC = 10 mg of oral morphine
Transdermal Fentanyl (TDF)	variable	25 µg/h of TDF = 60 mg of morphine approximately

3.3. Medicines with a similar therapeutic aim

The TARGINACT combination (oxycodone + naloxone), indicated for "severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut."
The actual benefit of this proprietary medicinal product is low for severe cancer-related pain and insufficient compared to existing therapies to justify it being paid for by public funds for other types of severe pain (Transparency Committee opinion of 07 December 2011, not marketed).

4 ANALYSIS OF AVAILABLE DATA/ UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

4.1.1. For cancer-related pain

The applicant has highlighted three new publications.[1,2,3]

- a meta-analysis (Reid 2006) which included four clinical trials that compared oral oxycodone to oral morphine (n = 3) and to hydromorphone (n=1). No difference was highlighted in terms of mean reduction in pain intensity between oxycodone and the other treatments;
- a randomised study (Mercadante 2010) in which no difference in analgesic efficacy was highlighted between oxycodone 20 mg/day and morphine 30 mg/day administered for 4 weeks to 66 patients with pain associated with pancreatic cancer;
- a systematic review of the literature (Nunez 2008) that evaluated the role of oxycodone in the management of neuropathic cancer pain

In summary, this new data did not change the assessment of the actual benefit of oxycodone for cancer-related pain, which remains substantial.

4.1.2. For non-cancer related pain

Context:
The extension of the indication for oxycodone to include non-cancer pain was obtained from Afssaps using a simplified procedure, taking into consideration:

- submission of pre-clinical genotoxicity data, as the absence of this data had led to restricting the initial marketing authorisation for oxycodone to cancer-related pain
- the fact that oxycodone is a strong opioid, like morphine, and its efficacy for severe pain regardless of the type is considered to have been demonstrated;
- the obtaining of a Marketing Authorisation by the same applicant within the context of a decentralised European procedure for TARGINACT, a fixed combination of oxycodone and naloxone, in the treatment of "severe pain, which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut", including non-cancer related pain.

Clinical data provided by the applicant
Within the scope of their request for the extension of the indication for reimbursable oxycodone-based proprietary medicinal products for non-cancer related pain, the applicant has provided several study reports from the Marketing Authorisation dossier and publications concerning the evaluation of the efficacy of oxycodone, administered either in the immediate-release or prolonged-release form:

- for acute, moderate to severe pain, in particular,
  - post-operative pain (5 to 15 mg for the IR form and 10 to 40 mg for the PR form, taken once),

1 Mercadante S et al. Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study. Clin J Pain 2010; 26: 794-797.
2 Reid C M et al. Oxycodone for Cancer-Related Pain. Arch Intern Med 2006; 166: 837-845.
3 Nunez Orlate JM. Oxycodone and the challenge of neuropathic cancer pain: a review. Oncology 2008; 74 (suppl. 1): 83-90.

- for moderate to severe chronic pain models, in particular:
  - rheumatic pain (osteoarthritis , low back pain) and chronic neck pain
  - neuropathic pain (diabetic, post-herpetic pain)
- Moderate to severe acute pain (post-operative pain)

Three publications were provided:

Systematic Cochrane review (2009)[4]
This systematic review evaluated the efficacy, the duration of action and the safety of a single dose of oxycodone either with or without paracetamol in the treatment of acute, moderate to severe post-operative pain. The review included twenty controlled, randomised, double-blind studies involving 2,641 patients (484 patients on oxycodone alone, 1,192 patients on oxycodone + paracetamol and 967 patients on placebo). In these studies, the patients were treated with:

- Immediate-release oxycodone (a dose of between 5 and 15 mg),
- prolonged-release oxycodone (a dose of between 10 and 30 mg),
- combination of paracetamol and oxycodone (oxycodone dose of between 5 and 15 mg and paracetamol dose of between 325 and 1000 mg),
- other analgesic treatments.

The proportion of patients seeing an improvement of at least 50% in their pain during the 4 to 6 hours after treatment was not statistically different between oxycodone 5 mg and the placebo (size of effect 1.26 [0.84, 1.88]). Oxycodone 15 mg was superior to the placebo for the endpoint of size of effect: 1.68 [1.22, 2.30]. The superiority of oxycodone combined with paracetamol compared with the placebo was demonstrated for all doses (oxycodone 5 mg + paracetamol 325 mg, oxycodone 10 mg + paracetamol 650 mg, oxycodone 10 mg + paracetamol 1000 mg). Adverse effects were more common with the combination than with the placebo. Overall, the efficacy of IR and PR oxycodone at doses higher than 5 mg was demonstrated in the treatment of post-operative pain.

NB:
The SPC recommends starting treatment with IR oxycodone at a dose of 5 mg for patients who have never been treated with strong opioids. However, this dose does not seem to be effective, given the results from the Cochrane meta-analysis.

Sunshine (1996), PR oxycodone versus IR oxycodone [5]
This controlled, randomised, double-blind trial evaluated the analgesic efficacy of PR oxycodone (10, 20, and 30 mg), compared with IR oxycodone (15 mg), oxycodone 10 mg combined with paracetamol 650 mg and placebo, taken once only in 182 patients with moderate to severe pain after abdominal or gynaecological surgery. As they were included in the systematic Cochrane review, the results were not described.

Curtis (1999), PR oxycodone versus PR morphine [6]
In this controlled, randomised, double blind trial, the analgesic efficacy of one dose of oral morphine (45 or 90 mg) and prolonged-release oxycodone (20 or 40 mg) was compared in 169 patients with moderate to severe pain following a hysterectomy. The patients received pethidine or an injection of morphine per-operatively; this treatment was stopped at least one hour before administration of the oral treatment. This trial showed that the analgesic power of

4 Gaskell H et al. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. Cochrane database of Systematic reviews 2009, Issue 3. Art. N°: CD002763. DOI: 10.1002/14651858.CD002763.pub2.
5 Sunshine A. et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. The Journal of Clinical Pharmacology 1996; 36: 595-603.
6 Curtis G.B. et al. Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. Eur J Clin Pharmacol 1999; 55: 425-429.

PR oxycodone was 1.8 times greater than that of PR morphine. Thus, within the scope of opioid treatment rotation, the initial dose of oxycodone should be half that of morphine. The adverse effects are those that are already recognised for other opioids.

Conclusions on the efficacy of oxycodone for post-operative pain:
It can be considered that, especially in light of the Cochrane meta-analysis of 2009, the efficacy of oxycodone at a dose greater than or equal to 10 mg taken once in the treatment of post-operative pain has been demonstrated. Its safety is comparable to other strong opioids.

- Moderate to severe chronic rheumatic pain: osteoarthritis

The applicant has provided three studies[7,8,9] which evaluated the efficacy of oxycodone in the treatment of osteoarthritis.

Markenson (2005)[7]
This randomised, double-blind placebo controlled trial evaluated the efficacy and safety of PR oxycodone 10 mg taken every 12 hours over 90 days in tablet form (n = 56) versus placebo (n = 51) in patients with osteoarthritis and suffering with moderate to severe pain in the week prior to inclusion, defined by a mean pain score of ≥ 5 (≥ 3 if the patient was treated with opioids) on an 11-point scale (0 = no pain and 10 = the worst pain imaginable). The patients were allowed to continue with their treatment with NSAIDs or corticosteroids.

The primary efficacy endpoints were:
- the mean pain intensity at 15 days (stable dose) and at 1 month (for patients who did not got a stable dose), measured using the brief pain inventory (BPI) which is a 32-point questionnaire including an anatomical diagram to pinpoint the pain and four numerical scales (0 to 10) relating to the intensity of the pain;
- the WOMAC index (Western Ontario and McMaster Universities Osteoarthritis Index) which is a self-assessment questionnaire of symptoms and physical disability linked to arthritis of the hip and/or the knee at 1 and 2 months;
- the percentage of patients who stopped treatment due to inadequate pain control.

The characteristics of the patients were comparable in the two groups on inclusion:
- the proportion of patients who received treatment with opioids previously was 65% with the placebo and 54% with oxycodone;
- the mean pain intensity measured using the BPI was 6.3 ± 0.2 with the placebo and 6.9 ± 0.2 with oxycodone.

After 15 days of treatment, the mean pain intensity scores on the BPI sub-scales at a stable dose were significantly lower in the oxycodone group (5.1 ± 0.3) compared with the placebo group (6.0 ± 0.3); p = 0.042. After 1 month, the same effect was observed: 4.9 ± 0.3 in the oxycodone group versus 5.8± 0.3 with the placebo; p = 0.022.
The difference of less than one point (0.9) on the BPI 11-point sub-scale, observed after 15 days and 1 month of treatment, evaluating the pain between PR oxycodone and placebo is low and is not clinically significant, with the difference being 1.1 points after 3 months of treatment (secondary end-point).
Function was measured using a sub-scale of the WOMAC index. This is a composite score (from 0 - 100), validated in the evaluation of osteoarthritis, which investigates three areas

7 Markenson JA et al. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomised controlled clinical trial. Clin J Pain 2005; 6: 524-535
8 Roth SH et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. Arch Intern Med 2000;160: 853-860.
9 Caldwell JR et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999; 26: 862-869.

(pain, functional incapacity and stiffness). The composite WOMAC score at 3 months was significantly improved with PR oxycodone (46.3 ± 2.7) in comparison to the placebo (62.9 ± 3.0), which is a reduction of 16.6 points on a 100-point scale, $p < 0.001$. Focusing specifically on function, a statistically significant difference in favour of oxycodone was highlighted: the score on the "function" sub-scale at 2 months was 46.1 ± 2.6 with PR oxycodone versus 59.1 ± 2.9 with the placebo, which is a difference of 13 points, $p < 0.001$.

The number of patients who stopped treatment prematurely was 38/51 in the placebo group (34 for ineffectiveness and 2 due to adverse effects) versus 33/56 in the oxycodone group (9 for ineffectiveness and 20 due to adverse effects).

Roth (2000)[8]

A randomised, double-blind placebo-controlled trial on 133 osteoarthritis patients suffering with moderate to severe pain receiving PR oxycodone 10 mg (n = 44), PR oxycodone 20 mg (n = 44) or placebo (n = 45) every 12 hours over 14 days.

The primary efficacy endpoint was the mean pain intensity, calculated based on self-assessment pain score using a four point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) at Weeks 1 and 2 and overall (mean of Weeks 1 and 2).
On inclusion, patients had a mean pain score of 2.4 ± 0.1 on placebo; 2.5 ± 0.1 on oxycodone 10 mg and 2.4 ± 0.1 on oxycodone 20 mg (four point scale). The proportion of patients previously treated with strong opioids was 60.9%.
The results for the 20 mg dosage were not presented, as the starting dosage for treatment with oxycodone is 10 mg according to the Marketing Authorisation.
No statistically significant difference was highlighted between oxycodone 10 mg and the placebo on the mean pain intensity score after 7 and 14 days of treatment: the mean pain intensity score was 2.02 at Week 1 on oxycodone versus 2.05 on placebo and 1.91 at Week 2 on oxycodone and 2.09 on placebo. There was also no statistically significant difference highlighted in functional incapacity between the two groups.
The number of patients who stopped treatment prematurely was 27/45 in the placebo group (22 for ineffectiveness and 2 due to adverse effects) versus 24/44 in the oxycodone 10 g group (12 for ineffectiveness and 12 due to adverse effects).

NB:
The duration of treatment is very short and does not correspond to that validated within the context of a chronic pain model. It should be noted that a medicinal product should be evaluated over a period lasting for 1 month or more to obtain an indication for the treatment of moderate to severe chronic pain (EMA Guidelines).

Caldwell (1999)[9]

The aim of this trial was to compare the efficacy of PR oxycodone administered every 12 hours with IR oxycodone combined with paracetamol administered four times per day in the treatment of osteoarthritic pain versus placebo.

One hundred and sixty-seven (167) osteoarthritis patients suffering from moderate to severe pain despite using NSAIDs were included in a initial open-label titration period of 30 days, during which they received a dose of IR oxycodone of between 20 and 60 mg; the mean dose at the end of this period was 40 mg per day. The intensity of pain measured using a four-point scale decreased by 1 point between inclusion and the end of the oxycodone IR titration period, going from 2.44 ± 0.04 to 1.38 ± 0.05 ($p = 0.0001$). The quality of sleep improved from 2.58 ± 0.08 to 3.57 ± 0.07 ($p = 0.0001$), on a five-point scale (1: very poor to 5, excellent).

Patients were then randomised to be treated over 30 days during a second double-blind phase with:

- PR oxycodone 10 mg twice daily (n = 34);
- IR oxycodone 5 mg + paracetamol 325 mg (n =37);
- or placebo (n = 36).

The superiority of the active treatments with regard to placebo has been proven:
During the second period (Week 2), the mean pain intensity was 1.41 in the PR oxycodone group versus 2.03 in the placebo group, p = 0.0003 (difference of 0.62 points on a four point scale). At Week 4, the mean pain intensity was 1.59 in the PR oxycodone group versus 2.08 in the placebo group, p = 0.0067 (difference of 0.49 points on a four point scale). There was also a statistical improvement in the quality of sleep on oxycodone compared with placebo.
No statistical difference was highlighted between the two active treatments in terms of efficacy and safety.
During the double-blind phase, 18/36 patients in the placebo group stopped treatment (13 due to ineffectiveness and 3 due to adverse effects) versus 7/34 in the PR oxycodone group (3 due to ineffectiveness and 3 due to adverse effects) versus 11/37 in the oxycodone IR/paracetamol group (4 due to ineffectiveness and 5 due to adverse effects).

Conclusions on the efficacy of oxycodone for moderate to severe osteoarthritic pain
Efficacy data for oxycodone in the treatment of osteoarthritic pain suggest that, at best, there is only a small effect (reduction in pain from 0.49 on a 4 point scale and 0.9 points on an 11 point scale) after a month of treatment. The numbers treatment withdrawals were significant in these studies.

- Moderate to severe chronic rheumatic pain: low back pain

The applicant has provided three studies, including two that have not been published, which evaluated the efficacy of oxycodone in the treatment of lower back pain.

Hale 1999[10]
This crossover study, which is of little relevance in the evaluation of the efficacy of oxycodone for chronic rheumatic pain, compared the efficacy of two pharmaceutical forms of oxycodone: PR 10 mg administered every 12 hours versus IR 5 mg 4 times per day in 47 patients with moderate to severe, constant, chronic low back pain despite the use of analgesics (including opioids for 80% of patients included). After an open-label titration phase lasting a maximum of 10 days (mean dose of oxycodone of 40 mg or less for 68% of patients), patients were included in a double-blind phase for 4 to 7 days. No difference was highlighted between the two forms in terms of pain control and safety.
The common adverse effects were: constipation, nausea, pruritus and drowsiness.

The applicant has also highlighted two unpublished studies that were included in the initial Marketing Authorisation dossier, and were re-submitted within the scope of the European mutual recognition procedure:

Study OC961002
In this randomised, double-blind study (carried out between January 1998 and May 1999), oxycodone 10 mg PR administered every 12 hours over a maximum of 3 months was compared with placebo in 110 patients with moderate to severe low back pain.
After a two-week titration phase, during which patients received oxycodone up to the point where their pain was stabilised, they were included in a randomised double-blind phase during which they received either oxycodone or placebo. No statistically significant difference

10 Hale ME et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. Clin J Pain 1999; 15: 179-183.

was highlighted between oxycodone and the placebo (4.7 ± 0.3 with oxycodone vs. 5.3 ± 0.3 with placebo) for the mean pain score or function score. The percentage of patients leaving the trial early due to inadequate pain control was significantly lower in the PR oxycodone group compared with the placebo group: 7/57 patients (12%) versus 21/51 patients (41%), $p < 0.001$.

Study OXCOCLIN0014
The aim of the study (carried out between June 1999 and August 2001), which is barely relevant in the evaluation of chronic pain, was to compare two pharmaceutical forms of oxycodone (IR as an oral solution vs. PR as tablets) in 245 patients. No difference was highlighted between the two forms in terms of pain reduction.

Conclusions on the efficacy of oxycodone for low back pain:
The data provided does not demonstrate the efficacy of oxycodone in the treatment of lowback pain; one study versus placebo shows a negative result for pain and function and the two other unpublished studies compare two different pharmaceutical forms of oxycodone.

- Moderate to severe rheumatic pain: acute pain episodes in chronic neck pain

Ma (2008)[11]
In this double-blind, randomised study the efficacy of PR oxycodone was compared to placebo in the treatment of acute pain episodes in chronic neck pain in 116 patients. For patients who had a score of between 4 and 6 on an 11-point visual analogue scale (VAS) (0 = no pain and 10 = the worst pain imaginable) at the inclusion appointment, the initial dose of PR oxycodone was 5 mg every 12 hours. For those patients with a score of between 7 and 10, the dose was 10 mg. After 3 days of treatment at the initial dose, a second appointment took place to readjust the dose, which either stayed the same, was increased by 25 to 50%, or was reduced by 25 to 50%, based on the results from pain evaluation. Severe peaks in pain were treated with 325 to 650 mg of paracetamol every 4 to 6 hours. Treatment duration was between 2 and 4 weeks.
Compared with inclusion, the frequency of acute pain episodes (68.97% in the placebo group and 56.89% in the oxycodone group; $p < 0.05$) and mean pain intensity (5.53 ± 1-25 in the placebo group versus 3.35 ± 1.57 in the oxycodone group $p < 0.05$) was statistically lower with oxycodone than with placebo from the third day of treatment. The results are confirmed at the 7th day for the two endpoints ($p < 0.05$).

A higher percentage of adverse effects were observed, especially nausea, constipation, pruritus and dizziness for patients treated with oxycodone compared with those receiving the placebo.

- Moderate to severe chronic pain: neuropathic pain in diabetic patients

Hanna (2008).[12]
This randomised, double-blind study compared the efficacy and safety of the combination of gabapentin and oxycodone PR (5 mg every 12 hours to 80 mg/day) versus gabapentin + placebo over 3 months in the treatment of moderate to severe neuropathic pain in 338 diabetic patients. According to the investigator, the majority of patients were treated with the maximum safe dose of gabapentin: 48% of patients in the oxycodone group and 43% of those in the placebo group were treated with a dose < 1200 mg per day; and 36% of patients in the oxycodone group and 39% of those in the placebo group were treated with a dose between 1200 mg and 1800 mg per day. After 12 weeks (3 months) of treatment, the

11 Ma K et al. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. Int J Clin Pract 2008; 6: 241- 247.
12 Hanna M et al. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. European Journal of Pain 2008; 12: 804-813.

reduction in pain intensity measured using the 11-point BPI sub-scale was significantly greater with gabapentin combined with oxycodone PR than with gabapentin alone: reduction of 2.1 points in the oxycodone/gabapentin group versus 1.5 points in the gabapentin/placebo group, which is a difference of 0.55 [0.15; 0.95], p = 0.007.
The proportion of patients who had an adverse event was 88% with oxycodone/gabapentin and 71% with placebo/gabapentin. The most common adverse events were gastrointestinal: 54% with oxycodone/gabapentin and 27% with placebo/gabapentin.
It should be noted that, according to SFETD guidelines [13] on the management of chronic neuropathic pain, gabapentin is recommended as a first-line treatment at a daily dose of between 1200 and 3600 mg.

Watson (2003)[14]
This study comparing PR oxycodone to benztropine, which is not actually available in France (but is in Canada), in 36 patients with diabetic neuropathy will not be described.

Gimbel (2003)[15]
In this randomised, double-blind study, oxycodone was compared to placebo in 159 patients with moderate to severe diabetic neuropathy. Patients received an initial dose of PR oxycodone of 10 mg every 12 hours or placebo; the dose of oxycodone could be increased every 3 days, up to a maximum 60 mg every 12 hours, or 120 mg per day over 6 weeks. The mean daily dosage of oxycodone PR across the whole study was 37 ± 21 mg. The reduction in pain intensity measured using the 11-point BPI sub-scale between Day 14 and Day 42 was statistically greater with oxycodone (-2.6 ± 0.28) than with placebo (-1.5 ± 0.29); p = 0.004. There were 19 patients who stopped the trial early with oxycodone, including 1 for ineffectiveness and 7 due to intolerance and 25 in the placebo group, including 11 for ineffectiveness and 4 due to intolerance. The most common adverse effects were: constipation (35 cases with oxycodone versus 11 with placebo), drowsiness (33 cases with oxycodone versus 1 with placebo) and nausea (30 cases with oxycodone versus 6 with placebo).

Finnerup (2005)[16]
This is a NNT (Number Needed to Treat) analysis of results expressed in terms of analgesic treatments, including oxycodone for post-herpetic nerve pain and diabetic neuropathy, based on the clinical studies detailed above (Watson 1998 and 2003, Gimbel 2003).

Conclusions on the efficacy of oxycodone for chronic and neuropathic pain in diabetics
Based on available data, the efficacy of oxycodone in the treatment of neuropathic pain in diabetic patients was demonstrated. The safety is that of a strong opioid.

- Moderate to severe chronic pain: post-herpetic neuropathy pain

Watson (1998)[17]
In this double-blind crossover study, 55 patients with post-herpetic pain were randomised to receive either PR oxycodone (10 mg every 12 hours as the initial dose, then the possibility of increasing the dose to a maximum of 30 mg every 12 hours) over 4 weeks. Thirty-eight (38) patients completed the study. Compared with placebo, the reduction in pain was more significant with oxycodone (2.9 ± 1.2 versus 1.8 ± 1.1, p = 0.0001).

13 Martinez V et al. Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecine ambulatoire. Recommendations for clinical practice of the French Society for the Study and Treatment of Pain. Douleurs Evaluation – Diagnostic – Traitement 2010; 11: 3-21.
14 Watson CP et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain 2003; 105: 71-78.
15 Gimbel JS et al. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology 2003; 60: 927-934.
16 Finnerup NB et al. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-305.
17 Watson CP et al. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998 50: 1837- 1841.

- Other data on non-cancer related pain (systematic reviews)

Noble[18](2008) and Papaleontiou[19] (2010)
Two systematic reviews of the literature evaluating oxycodone were provided. Only details of the review by Papaleontiou, the most recent and including the largest number of studies (n = 9), will be described.
In this systematic review including 9/18 randomised, controlled clinical studies that evaluated the effect of opioids in non-cancer related pain (osteoarthritis 70%, neuropathic pain 13% and other pain 17%).
The mean age of patients included was 64 years and the mean treatment duration was 4 weeks.
Reduction in pain was - 0.557 ($p < 0.001$) and reduction in functional incapacity was - 0.432 ($p < 0.001$).
The most common adverse events were: constipation (30%) and nausea (28%). Treatment was stopped prematurely by 25% of patients.

- Other efficacy data

Gatti (2009)[20]
The results of this open-label study which had a poor quality method, suggest that there is a benefit to immediate- and prolonged-release oral forms in the treatment of chronic cancer-related and non-cancer-related pain.

4.2. Adverse effects

Safety data from the studies provided[21,22] did not identify any new signs of safety issues.

Portenoy (2007) [21]
The results at Year 3 of this non-comparative follow-up registry of certain patients who participated in studies evaluating the efficacy of PR oxycodone in the treatment of pain linked to osteoarthritis, low back pain and diabetic neuropathy.
Given the method (absence of comparison), only the safety results are taken into consideration. The adverse effects were those expected for a strong opioid: constipation (15% of patients), nausea (12%), drowsiness (8%), vomiting (7%) and depression (2%). Among the serious AEs, seven deaths were observed during the study.

Ytterberg (1998)[22]
In this American retrospective cohort study, prescriptions of opioids (oxycodone and codeine) recorded in a pharmaceutical database over 3 years were analysed. Thirty-eight percent of patients had adverse effects, the most common being: nausea, dyspepsia, constipation and sedation.

Pharmacovigilance data:
During the period of 13 April 2010 to 12 April 2011 (1 year), no new safety concerns were identified on an international level or in France.
More than 79% of adverse events concerned:
- General disorders and administration site conditions (26%)
- Psychiatric disorders (24%)

18 Noble M et al. Long-term opioid therapy for chronic non-cancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage 2008; 35: 214-228.
19 Papaleontiou M et al. Outcomes associated with opioid use in the treatment of chronic non cancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2010; 58: 1353-1369.
20 Gatti A et al. Adequacy assessment of oxycodone/paracetamol (acetaminophen) in multimodal chronic pain: a prospective observational study. Clin Drug Investig 2009; 29: 31-40.
21 Portenoy RK et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain 2007; 23: 287-299.
22 Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. Arthritis Rheum 1998; 41: 1603-1612.

- Gastrointestinal disorders (12%)
- Injuries, poisoning and complications linked to procedures (10%)
- Nervous system disorders (7%).

For information purposes, a request to amend section 4.8 "Adverse effects" of the SPC of oxycodone-based proprietary medicinal products such as morphine and hydromorphone has been in the process of being evaluated by AFSSAPS (then ANSM) since January 2009.
Following a European arbitration procedure concerning the interaction between alcohol and prolonged-release forms of morphine, oxycodone and hydromorphone, (Decision of European Commission of 20 April 2011), an amendment to the SPC of oxycontin PR is also in the process of being evaluated by ANSM.
Oxycodone, as with all narcotics, can give rise to inappropriate or abusive use.
In summary, the data provided did not identify any new safety signal comparing to known safety profile of this strong opioid.

4.3. Conclusion

The efficacy of oxycodone, in immediate and prolonged-release forms, has been studied in severe cancer-related and non-cancer related pain.
For severe cancer-related pain, data provided confirm that the efficacy and safety of oxycodone are comparable to that of morphine.

For severe non-cancer related pain, the conclusions vary according to the type of pain model studied:
- for acute post-operative pain, the efficacy of oxycodone (single dose ≥ 10 mg), was demonstrated, in particular through the Cochrane meta-analysis of 2009;
- for diabetic neuropathic pain and post-herpetic pain, based on available data, the efficacy of oxycodone has been demonstrated;
- for pain linked to osteoarthritis, available data suggests an efficacy that is, at best, clinically modest. After one month of treatment, the level of effect (reduction of 0.49 points on a 4 point scale and 0.9 points on an 11-point scale) is low and the number of patients stopping treatment is substantial;
- for low back pain, the available data (including a negative study versus placebo) did not demonstrate the efficacy of oxycodone in controlling or in improving functional disability;
- for acute episodes of neck pain, oxycodone as a short-term treatment significantly reduced the frequency and the intensity of pain compared with placebo from the 3rd day of treatment. The results are confirmed at the 7th day for the two endpoints.

For oxycodone, as with all narcotics, there is a risk of dependency which should be considered if taking this medicinal product in the long term.

In summary, the transparency Committee considers that:
- for chronic rheumatic pain, the efficacy/adverse effects ratio for oxycodone is poorly established, given the results from the clinical studies that do not formally show its clinical benefit, its adverse effects and the risk of dependence,
- for acute post-operative pain and for severe, chronic neuropathic pain, the efficacy/adverse effects ratio of oxycodone is similar to that of morphine.

5 MEDICINAL PRODUCT USAGE DATA

Data was only supplied for the proprietary medicinal products included on the list of medicines refundable by National Health Insurance (OXYCONTIN PR, OXYNORM and OXYNORMORO).
According to IMS-EPPM data (moving annual total February 2012), 141,000 prescriptions for OXYCONTIN PR were issued; the mean daily dosage was two tablets and the prescription duration was 26.1 days.
There were 37,000 prescriptions issued for OXYNORM and 9,000 prescriptions for OXYNORMORO. This low number of prescriptions will not enable a qualitative analysis of data to be carried out.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit/ re-assessment of actual benefit

For cancer-related pain
Severe cancer-related pain can lead to a very marked deterioration in quality of life.

These proprietary medicinal products are intended as symptomatic treatment.

These medicinal products are first- or second-line therapies.

Available efficacy and safety data have not shown a difference between oxycodone and morphine. The efficacy/adverse effects ratio for these medicinal products remains high.

> Public health benefit
> Given their frequency and the psychosocial repercussions (fatigue, anxiety, depression), severe cancer-related pain represents a moderate to substantial burden on public heath.
> Improved management of intense chronic pain is a public health need that is an established priority (GTNDO* priority in the management of pain).
> For severe cancer-related pain, in view of the available data versus morphine, oxycodone is not expected to have an additional impact on morbidity. In the absence of available data, the impact of oxycodone on the quality of life of patients treated is not quantifiable. In addition, a negative impact due to the common adverse effects of strong opioids and their impact on quality of life and day-to-day activities of patients cannot be ruled out.
> Furthermore, oxycodone, a possible alternative to morphine for severe cancer-related pain, only provides a partial response to an identified public health need.
> In summary, it is expected that the public heath benefit of oxycodone is low for cancer-related pain.

There are treatment alternatives, in particular, other strong opioids.

The actual benefit of these proprietary medicinal products **remains substantial** in the treatment of cancer-related pain, which can be adequately managed only by opioid analgesics.

* Groupe Technique National de Définition des Objectifs [National technical group for setting of public-health objectives] (DGS [Directorate General for Health]-2003)

For non-cancer-related pain

- Severe, acute pain (post-operative pain)

Severe, acute post-operative pain can lead to a very marked deterioration in quality of life.

These proprietary medicinal products are intended as symptomatic treatment.

As strong opioids, these medicinal products are first-line treatments in the management of severe, acute pain.

The efficacy of oxycodone has been demonstrated in the treatment of post-operative pain. Its safety is comparable to that of other strong opioids.

The efficacy/adverse effects ratio is high.

Public health benefit

Given its frequency, severe post-operative pain represents low to a moderate burden on public health.

Improved management of intense chronic pain is a public health need that is an established priority (GTNDO* priority in the management of pain).

For severe post-operative pain, in view of the available data, oxycodone is not expected to have an additional impact on morbidity. In the absence of available data, the impact of oxycodone on the quality of life of patients treated is not quantifiable. In addition, a negative impact due to the common adverse effects of strong opioids and their impact on quality of life and day-to-day activities of patients cannot be ruled out.

Furthermore oxycodone, for post-operative pain only provides a partial response to an identified public health need.

In summary, it is expected that the public heath benefit of oxycodone is low for post-operative pain.

There are treatment alternatives, in particular, other strong opioids.

The actual benefit of these proprietary medicinal products **is substantial**.

- Severe chronic pain: neuropathic pain

Neuropathic pain is a chronic condition. Neuropathic pain can appear in many clinical situations: for example in diabetic neuropathy, secondary to shingles, herpes, HIV or a stroke, after an amputation (phantom limb pain), or following surgery or trauma. Neuropathic pain can be spontaneous, combining the occurrence of both breakthrough pain (like an electric shock) and persistent, underlying pain (burning sensations). It may also be provoked. Sensory disorders may occur in association. Such pain can cause significant psychosocial impairment (fatigue, anxiety, depression) and impact quality of life.

These proprietary medicinal products are intended as symptomatic treatment.

Neuropathic pain does not react predictably to opioid treatment. It is, according to the available guidelines, a second-line treatment, after failure of a first-line therapy (tricyclic anti-depressants or anti-epileptic medication).

The efficacy of oxycodone was demonstrated in the treatment of diabetic and post-herpetic neuropathic pain. Its safety is comparable to that of other strong opioids. The efficacy/adverse effects ratio for these medicinal products is high.

Public health benefit

Given its frequency and the psychosocial repercussions (fatigue, anxiety, depression), severe neuropathic pain represents a substantial burden on public heath.

Improved management of intense chronic pain is a public health need that is an established priority (GTNDO* priority in the management of pain).

For severe neuropathic pain, in view of the available data (versus an active comparator medicine or placebo), oxycodone is not expected to have an additional impact on morbidity. In the absence of available data, the impact of oxycodone on the quality of life of patients treated is not quantifiable. In addition, a negative impact due to the common adverse effects of strong opioids and their impact on quality of life and day-to-day activities of patients cannot be ruled out (work and driving in particular).

Furthermore, oxycodone for severe neuropathic pain, does not provide a response to an identified public health need.

In summary, it is not expected that oxycodone will be of public health benefit for neuropathic pain.

There are treatment alternatives.

The actual benefit of these proprietary medicinal products is **substantial.**

- Severe, chronic rheumatic pain: osteoarthritis, low back pain and neck pain.

Osteoarthritis and low back pain are both chronic inflammatory conditions that can lead to deterioration in quality of life.

These proprietary medicinal products are intended as symptomatic treatment.

In view of the available data, the efficacy of oxycodone is inconsistent, and at best modest or not established in the treatment of osteoarthritis and low back pain. It was not evaluated for specific algo-functional endpoints.

Adverse effects were common and led to a significant number of patients stopping treatment in clinical studies. There is a risk of pharmaceutical dependence.

Consequently, the efficacy/adverse effects ratio for these proprietary medicinal products is poorly established for low back pain and osteoarthritis.

Public health benefit

Given its frequency and the psychosocial repercussions (fatigue, anxiety, depression), severe rheumatic pain represents a moderate to substantial burden on public heath.

Improved management of intense chronic pain is a public health need that is an established priority (GTNDO* priority in the management of pain).

For severe rheumatic pain, in view of the available data (low analgesic effect and absence of comparative data on alternative available treatments), oxycodone is not expected to have an additional impact on morbidity. In the absence of available data, the impact of oxycodone on the quality of life of patients treated is not quantifiable. In addition, a negative impact due to the common adverse effects of strong opioids and their impact on the quality of life and day-to-day activities of patients (work and driving, in particular), especially elderly patients, cannot be ruled out.

Furthermore, for rheumatic pain, oxycodone does not provide a response to an identified public health need.

* Groupe Technique National de Définition des Objectifs [National technical group for setting of public-health objectives] (DGS [Directorate General for Health]-2003)

In summary, it is not expected that oxycodone will be of public health benefit for rheumatic pain.

Given their adverse effects, the risk of dependency and, above all the results from studies published in the literature that show inconsistent efficacy, which is at best modest and does not demonstrate certain pertinent endpoints, the Transparency Committee considers that oxycodone-based proprietary medicinal products do not have a place in the treatment of chronic rheumatic pain.

In view of all these factors, the actual benefit of these proprietary medicinal products in comparison with the treatments that are already available for this type of pain **is not sufficient** to justify reimbursement by National Health Insurance.

6.2. Improvement in actual benefit (IAB)

OXYCONTIN, OXYNORM and OXYNORMORO do not provide an improvement in actual benefit (IAB V) in comparison with immediate- and prolonged-release morphine-based products in the management of severe cancer-related, post-operative and neuropathic pain.

6.3. Therapeutic use

Cancer-related pain

In the treatment of moderate to severe cancer-related pain, morphine is the step III opioid recommended by the WHO to be used as a first-line treatment in adults (standard, expert agreement). [23]

According to ANAES[24] recommendations:

"In agreement with WHO guidelines, it is recommended that oral medication is used in preference to other forms, that analgesia be taken as a preventive measure, rather than when pain occurs, that treatment is tailored to suit the patient, that effects are re-evaluated regularly (a minimum of once daily until effective analgesia is achieved), that the patient and their immediate family are informed of any potential adverse effects of treatment and to provide all the means that will enable them to have and use analgesics according to the three step strategy.

For cases of treatment with strong opioids, it is recommended to start with immediate-release morphine sulfate or possibly the prolonged-release form. For elderly patients requiring doses below 5 milligrams per dose, morphine hydrochloride solution is useful.

Once the daily effective dose of morphine is determined (morphine titration), a change may be proposed to either a prolonged-release oral form of morphine (morphine sulfate), or transdermal fentanyl (patch). In addition to the basic treatment, it is recommended to use a supplementary analgesic with a fast action morphine product (interdose).

In cases where treatment with oral morphine has failed, the patient must be carefully re-evaluated and specifically investigate the neurogenic mechanism of action or significant emotional or cognitive factors.

If this pain is purely nociceptive, in cases of failure of treatment due to unmanageable adverse effects with morphine, it is recommended to either change to a different opioid (rotation of opioids), or change the method of administration.

If the use of oral medication is not possible, it is recommended to change to an injectable form, either a sub-cutaneous or intravenous injection if the patient has an injection chamber implant or a venous catheter, or change to transdermal fentanyl (patch)."

[23] National Federation of French Comprehensive Cancer Centers: Standards, Options and Recommendations 2002 for analgesic medicinal products for cancer-related pain due to excess nociception in adults, updated.

[24] Methods of managing adults who require palliative care - ANAES / Occupational recommendations and references department / December 2002

Acute non-cancer-related pain

Following the withdrawal of dextropropoxyphene-based combinations, in 2010 AFSSAPS published an update,[25] which was then further updated in 2011, on the management of moderate to intense pain in adults. This update states that for intense, acute nociceptive pain (especially acute post-traumatic, post-surgical, rheumatic, and gynaecological pain) treatment may call for weak or step III opioids for very intense pain, depending on the urgency to achieve relief and the clinical situation.

Guidelines for post-operative pain (SFAR 2008)[26, 27]

According to the French Society of Anaesthesia and Intensive Care (SFAR) consensus conference on the management of post-operative pain updated in 2008, "the parenteral route is widely used in the perioperative period. It is nontheless recommended to only use sub-cutaneous and intravenous methods for patients who can not take oral medication. It is recommended to use immediate-release oral morphine in immediate post-operative periods or when changing from parenteral analgesia. In practice, treatment can start at the same time as oral feeding is recommenced. However, there is no place for oral morphine titration during the immediate post-operative period. IV titration is preferred.
Oral morphine products are an effective emergency treatment in combination with multimodal analgesia. For example, oral oxycodone may be an alternative to morphine for post-operative surgical pain (without Marketing Authorisation).

The MAPAR 2010 guidelines stated that for the management of post-operative pain, morphine remains the most used strong opioid post surgery.[27] Oxycodone is an alternative with an equivalent efficacy.

Chronic non-cancer related pain

The management of this type of pain is multimodal, including treatment of the causal disease, analgesic medicinal and non-medicinal treatments and treatment of psychological, social and professional aspects.
While strong opioids have been shown to be effective and are widely used for acute, post-surgical and cancer-related pain, their use for chronic non-cancer related pain remains controversial, due to the adverse effects and uncertainties concerning safety and dependency and, above all, as there are very few published studies in the literature confirming their efficacy in this indication.

The Afssaps 2004 update[28] on the place of strong opioids in the treatment of chronic non-cancer related pain (CNCRP) states that "while the benefit of treatment with strong opioids is recognised now in the treatment of chronic nociceptive cancer-related pain, the risk/benefit ratio of such a prescription in the treatment of chronic non-cancer related pain (CNCRP) should be carefully evaluated, to avoid the use of a medicinal product that may have little or no effect, or that may lead to harmful adverse effects, even resulting in the patient developing a physical and/or psychological dependence". It is also indicated that "certain chronic pain syndromes are barely sensitive to opioids and will not be indicated" and that "it must be ensured that the somatic cause is clearly identified, that the pain is intense, not sufficiently controlled by a etiologic treatments and that “standard” analgesic treatments (other than strong opioids) are ineffective when they are correctly prescribed and evaluated. Opioid treatment should be integrated into a global treatment plan, including other medicinal and non-medicinal treatments (psychotherapy, physical treatment and physiotherapy)."

25 AFSSAPS Update – Managing moderate to intense pain – 2010/2011
26 Professional information. Guidelines formalised by experts 2008. Management of post-operative pain in children and adults. SFAR pain - loco-regional anaesthesia committee and the standards committee. Annales Françaises d’Anesthésie et de Réanimation 2008; 27: 1035-1041.
27 MAPAR. 2010
28 Update of the good use guidelines for strong opioids in the treatment of non-cancer relate pain. AFSSAPS. 2004

Neuropathic pain[29,30]

Neuropathic pain does not or barely responds to treatment with standard analgesics (NSAIDs, paracetamol, aspirin).

Analgesic treatment of neuropathy with medication is based on the consensual use of tricyclic anti-depressants or on the use of anti-epileptic medication acting on the sodium or calcium channels. These treatments have a moderate efficacy. Their safety profile may limit their prescription. Responders to the different treatments are still not well identified.

Since the efficacy of treatments is often only partial, combinations of analgesics with complementary mechanisms of action may be proposed.

According to the French society for the Study and Treatment of Pain (SFETD) guidelines published in 2010, strong opioids, including oxycodone, are recommended in the treatment of chronic neuropathic pain (non-cancer related) after failure of first-line treatments (tricyclic anti-depressants or anti-epileptics) used as monotherapy and, if required, as part of a combination.

The efficacy of strong opioids (oxycodone, morphine and methadone) is established for peripheral neuropathic pain, especially if it is diabetic or post-herpetic (Grade A). The doses necessary to achieve this efficacy are often high and require individual titration. The prescription of strong opioids for chronic non-cancer related pain should only be proposed after failure of other available treatments following standard precautions for use of morphine-based products in the long term (professional agreement, Afssaps update 2004). The risk of abuse was estimated at 2.6% in a systematic review.

29 V. Martinez et al. French Society for the Study and Treatment of Pain. Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecine ambulatoire. Recommendations for clinical practice of the French Society for the Study and Treatment of Pain. Douleurs 2010;11: 3-21.

30 V. Martinez, M. Lantéri-Minet. Traitements pharmacologiques actuels, recommandations et perspectives des douleurs neuropathiques. Douleur analg 2010; 23 : 93-98

6.4. Target population

The target population of oxycodone-based proprietary medicinal products (OXYCONTIN PR, OXYNORM and OXYNORMORO) is represented by adult patients suffering from severe cancer-related pain, severe, acute post-operative pain and severe, chronic neuropathic pain that can only be treated with strong opioids.

Severe cancer-related pain:
According to a projection made by INVS,[31] in 2011 the number of new cases of cancer was estimated at 207,000 in men and 158,500 in women, which is a total of 365,500 cases.
From the results of a European survey on the use (European survey on cancer pain - EPIC)[32] carried out in 2007, including 642 French patients with cancer, it can be estimated that 43% of these patients had severe pain at one point during their illness, i.e. 157,200 patients.

Severe, chronic neuropathic pain:
The sub-population suffering with severe neuropathic pain and who are being treated with a strong opioid as a second-line treatment may be calculated based on the following sources:
According to INSEE, on 1st January 2012, the French adult population (≥ 18 years) was 49,551,871. The prevalence of peripheral and central neuropathic pain may be estimated as 1%[33], which is approximately 495,519 patients in France.
According to the results of an epidemiological study,[18] 79% of patients are treated with either anti-epileptics, anti-depressants or opioids and 41% of these patients achieve only limited pain relief with these treatments.
Thus, the target population for oxycodone may be estimated as a maximum of 392,000 patients for neuropathic pain.

Severe, acute post-operative pain:
In the absence of epidemiology data, it is not possible to quantify the target population.

6.5. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services for severe cancer-related pain.
The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services for severe pain and severe chronic neuropathic pain.

The Transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services for chronic non-cancer pain and not neuropathic.

6.5.1. Packaging: Appropriate for the prescription conditions

6.5.2. Reimbursement rate: 65%

31 INVS: Projection of the incidence and the mortality of cancer in France in 2010. http://www.invs.sante.fr/applications/cancers/projections2010/rapport_projections_nationales_cancer_2010.pdf
32 H. Breivik et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Annals of oncology 2009; 20: 1420-1433.
33 EPAR Lyrica.