HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

15 October 2014

OXYCONTIN PR 5 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 366 903 4 9)

OXYCONTIN PR 10 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 354 209 0 9)

OXYCONTIN PR 15 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 384 584 4 2)

OXYCONTIN PR 20 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 354 215 0 0)

OXYCONTIN PR 30 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 384 587 3 2)

OXYCONTIN PR 40 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 354 222 7 9)

OXYCONTIN PR 60 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 384 598 5 2)

OXYCONTIN PR 80 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 354 294 8 3)

OXYCONTIN PR 120 mg, prolonged-release film-coated tablet
B/28 (CIP: 34009 384 602 2 3)

OXYNORM 5 mg, capsule
B/14 (CIP: 34009 362 419 0 9)

OXYNORM 10 mg, capsule
B/14 (CIP: 34009 362 421 5 9)

OXYNORM 20 mg, capsule
B/14 (CIP: 34009 362 423 8 8)

OXYNORM 10 mg/ml, oral solution
30 ml bottle with graduated syringe for oral administration (CIP: 34009 366 912 3 0)

OXYNORM 10 mg/ml, solution for injection
B/5 1 ml ampoules (CIP: 34009 366 914 6 9)

OXYNORM 10 mg/ml, solution for injection
B/5 2 ml ampoules (CIP: 34009 366 915 2 0)

OXYNORM 10 mg/ml, solution for injection
B/4 20 ml ampoules (CIP: 34009 392 317 1 6)

OXYNORM 50 mg/ml, solution for injection
B/5 1 ml ampoules (CIP: 34009 387 625 3 2)

OXYNORMORO 5 mg, orodispersible tablet
B/14 (CIP: 34009 380 421 3 9)
OXYNORMORO 10 mg, orodispersible tablet
B/14 (CIP: 34009 380 425 9 7)
OXYNORMORO 20 mg, orodispersible tablet
B/14 (CIP: 34009 380 428 8 7)

Applicant: MUNDIPHARMA

INN	Oxycodone
ATC code (2013)	N02AA05 (natural opium alkaloids)

Reason for the review	**Reassessment of Actual Benefit at the request of the applicant in compliance with article R-163-12 of the French Social Security Code.**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) except for the injectable forms **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**Indications concerned by the reassessment: chronic non-cancer and non-neuropathic pains**

Actual Benefit	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. Oxycodone-based medicinal products should be used as little as possible, after failure of other pharmacological and non-pharmacological treatments (including physiotherapy) recommended in these indications. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.
Therapeutic use	Oxycodone-based proprietary medicinal products may be considered as a last-resort treatment in osteoarthritis of the hip or knee, in case of severe intractable pain episodes, at a stage where surgery is planned and in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery, for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. These medicinal products should be used as little as possible, after failure of other recommended pharmacological and non-pharmacological treatments (including physiotherapy). Oxycodone-based medicinal products may be considered as a last-resort treatment in chronic lumbar pain, in case of severe intractable pain flares and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. These medicinal products should be used as little possible, after failure of other recommended pharmacological and non-pharmacological treatments (including physiotherapy). In all cases, the use of an oral form is preferred. The decision to prescribe oxycodone, as for other strong opioids, must be made in consideration of its safety profile and the potential risk of misuse or abuse. In the absence of clinical data, oxycodone-based proprietary medicinal products have no role in the therapeutic management of osteoarthritis of the fingers. With the exception of severe intractable pain in mechanical rheumatic diseases like osteoarthritis of the knee or hip and chronic lumbar pain and under the conditions specified above, oxycodone-based proprietary medicinal products have no role in the therapeutic strategy for chronic non-cancer and non-neuropathic pain, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date of Marketing Authorisation (national procedure): OXYCONTIN PR 5 mg: 14 March 2005 OXYCONTIN PR 10 mg, 20 mg, 40 mg, 80 mg: 5 December 2000 OXYCONTIN PR 15 mg, 30 mg, 60 mg, 120 mg: 11 March 2008 OXYNORM 5 mg, 10 mg, 20 mg: 11 June 2003 OXYNORM 10 mg/ml, oral solution: 22 March 2005 OXYNORM 10 mg/ml, solution for injection, 1 ml and 2 ml ampoules: 16 March 2005 OXYNORM 10 mg/ml, solution for injection, 20 ml ampoules: 23 January 2009 OXYNORM 50 mg/ml: 19 August 2008 OXYNORMORO 5 mg, 10 mg: 19 July 2007

	OXYNORMORO 20 mg: 16 July 2007
Prescribing and dispensing conditions/special status	Oral forms: Narcotic medicine, dispensing limited to 28 days Injectable forms: Narcotic medicine, dispensing limited to 7 days, or 28 days when administered via an active infusion system.
ATC Classification	2013 N Nervous system N02 Analgesics N02A Opioids N02AA Natural opium alkaloids N02AA05 Oxycodone

02 BACKGROUND

In its opinion of 19 September 2012 for renewal of inclusion and extension of indication to non-cancer pain for the proprietary medicinal products OXYCONTIN PR, OXYNORM and OXYNORMORO, the Transparency Committee concluded that in severe chronic rheumatic pain: osteoarthritis, lumbar pain and neck pain, the actual benefit of these proprietary medicinal products was **insufficient**, given the existing therapies, to justify National Health Insurance reimbursement in this type of pain.
Furthermore, the Committee concluded that the actual benefit of these proprietary medicinal products remained **substantial** in the treatment of severe cancer pain which can be adequately managed only with opioid analgesics, in severe acute non-cancer pain (postoperative pain) and severe chronic neuropathic pain.
Mundipharma is requesting a reassessment of the level of actual benefit in severe chronic rheumatic pain for OXYCONTIN PR, OXYNORM and OXYNORMORO.

03 THERAPEUTIC INDICATIONS

“Treatment of severe pain which can be adequately managed only with strong opioid analgesics, in particular cancer pains.”

04 DOSAGE

"For adult use only.

- ✓ Oral forms

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: use the dose of 10 mg every 12 hours (OXYCONTIN PR), 5 mg every 4 to 6 hours (OXYNORM, OXYNORMORO);

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 the treatment at the lowest dose, 5 mg every 12 hours, 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 increased 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 an immediate release form to a prolonged-release form, the daily dosage should remain unchanged.

Discontinuation of treatment

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

- ✓ Injectable forms

Treating chronic cancer pain:

IV and subcutaneous 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; continuous infusion at the normal dosage is combined with a self-administered 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 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 may be advisable to taper the oxycodone dose gradually to prevent symptoms of withdrawal."

05 THERAPEUTIC NEED

A comprehensive assessment of the pain experienced is an essential prerequisite for pain management.[1]
The severity of the pain is assessed by self-assessment using a validated scale (visual analogue scale (VAS), numerical scale or simple verbal scale). On the VAS, pain is classed as moderate when it is rated higher than 4 and intense when it is rated higher than 7. There is no direct link between the value obtained on a scale and the type of analgesic treatment necessary. Scores calculated using one of these scales have descriptive value in a given individual and allow the pain and efficacy of treatment to be monitored. Other scales are specific to a particular population; for example, the DOLOPLUS scale is adapted for elderly patients who have difficulty with verbal communication.
The choice of analgesic treatment is guided by the intensity of the pain and whether it is acute or chronic.
There are numerous options for pain management, some involving drug therapy and some not.

Analgesic treatments are divided into three groups:[2]
- **Step 1 analgesics** or peripheral analgesics: paracetamol, acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen at analgesic doses. These are usually indicated in the symptomatic treatment of mild to moderate pain.
- **Step 2 analgesics** are indicated in the symptomatic treatment of moderate to intense pain. These are the weak opioids (codeine, tramadol, dihydrocodeine and low-dose opium) mostly marketed in combination with a peripheral analgesic, most often paracetamol.
- **Step 3 analgesics** are indicated in intense pain and/or pain resistant to weaker analgesics. They include strong pure opioid agonists (morphine, pethidine, fentanyl, hydromorphone, oxycodone), partial agonists (buprenorphine), agonist-antagonists (nalbuphine), with a μ-opioid agonist activity and additional properties of inhibiting the reuptake of noradrenaline (tapentadol).

When choosing an analgesic treatment, efficacy should be considered relative to contraindications, precautions for use and the potential adverse effects.

[1] AFSSAPS [French Healthcare Product Safety Agency]. SFR [French Society of Rheumatology]. SFETD [French Society for the Study and Treatment of Pain]. Prise en charge des douleurs de l'adulte modérées à intenses [Management of moderate to intense pain in adults]. Mise au point. [Focus] Actualisation. [Update] May 2011.
[2] AFSSAPS Mise au point sur le bon usage des opioïdes forts dans le traitement des douleurs chroniques non cancéreuses 2004 [Focus on the proper use of opioids in the treatment of chronic non-cancer pain 2004].

Strong opioids may be used:

- as a short-term treatment for the most intense acute pain (postoperative pain, myocardial infarction, renal colic, radicular pain, painful acute exacerbations of a chronic condition, etc.);
- as an extended treatment, in chronic pain due to excess nociception resistant to step 1 and 2 analgesics. Concerned are cancer pain, as soon as the pain intensity requires it without awaiting the end of life and some non-cancer pain resistant to all forms of treatment (neuropathic pain, etc.).

This evaluation covers the management of chronic non-cancer and non-neuropathic pain, notably including rheumatic pain occurring in the context of lumbar pain and osteoarthritis.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

These include the other strong opioids (WHO step 3) on the list of proprietary medicinal products reimbursed and marketed (see appendix tables of the assessments by the Transparency Committee of the actual benefit in non-cancer and non-neuropathic pain).

06.2 Other health technologies

According to the type of pain, there are several non-pharmacological alternatives: physical training, physiotherapy, acupuncture, orthotics, hydrotherapy, electrotherapy, transcutaneous nerve stimulation and traction. Prosthetic replacement surgery is an alternative at the most advanced stages of knee and hip osteoarthritis.

◗ Conclusion

The pharmacological comparators listed are clinically relevant.

07 SUMMARY OF PREVIOUS ASSESSMENTS

Before 9 July 2010, the indications for the proprietary medicinal products OXYCONTIN PR on the one hand, and OXYNORM and OXYNORMORO were different:

- Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years) for OXYCONTIN PR,
- Cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years) for OXYNORM and OXYNORMORO.

Since 9 July 2010, oxycodone hydrochloride-based proprietary medicinal products have had their indications worded the same way, i.e., the treatment of severe pain which can be adequately managed only with strong opioid analgesics, in particular cancer pain.

Assessments of OXYCONTIN PR proprietary medicinal products prior to the change in the marketing authorisation wording of 9 July 2010

Date of opinion (reason for the request)	20 June 2001 Listing of 10, 20, 40 and 80 mg tablets
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	OXYCONTIN PR, prolonged-release film-coated tablet does not provide any improvement in actual benefit compared with sustained release morphine.
Studies requested	-

Date of opinion (reason for the request)	7 September 2005 NHI/Hospital Use listing 5 mg tablets
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	OXYCONTIN PR 5 mg, does not provide an improvement in actual benefit relative to OXYCONTIN PR 10 mg, 20 mg, 40 mg and 80 mg.
Studies requested	-

Date of opinion (reason for the request)	3 January 2007 Renewal of inclusion 5 mg, 10 mg, 20 mg, 40 mg, 80 mg
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	-
Studies requested	-

Date of opinion (reason for the request)	3 September 2008 NHI/ Hospital Use listing of 15, 30, 60 and 120 mg tablets
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	The new doses of OXYCONTIN PR do not provide any improvement in actual benefit (IAB V) relative to the existing doses.
Studies requested	-

Assessments of OXYNORM proprietary medicinal products prior to the change in the marketing authorisation wording of 9 July 2010

Date of opinion (reason for the request)	26 November 2003 NHI/ Hospital Use listing of 5, 10 and 20 mg capsules
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	OXYNORM provides no 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 sulfate.
Studies requested	-

Date of opinion (reason for the request)	16 March 2005 Hospital Use listing of the 10 mg/ml solution for injection, 1 ml ampoules, B/5 and 2 ml ampoules, B/5
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	No improvement in actual benefit compared with other injectable morphines.
Studies requested	-

Date of opinion (reason for the request)	7 September 2005 Hospital Use listing of 10 mg/ml oral solution, one 30 ml glass bottle with syringe for oral administration
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	OXYNORM 10 mg/ml, oral solution does not provide an improvement in actual benefit compared with OXYNORM 5 mg, 10 mg and 20 mg, capsule.
Studies requested	-

Date of opinion (reason for the request)	3 January 2007 Renewal of inclusion for 5, 10 and 20 mg capsules.
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	-
Studies requested	

Date of opinion (reason for the request)	29 October 2008 Hospital Use listing for the 50 mg/ml solution for injection, 1 ml ampoules, B/5
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	OXYNORM, 50 mg/ml solution for injection does not provide any improvement in actual benefit (IAB V).
Studies requested	-

Date of opinion (reason for the request)	1st April 2009 Hospital Use listing for the 10 mg/ml solution for injection, 20 ml ampoules, B/4
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	This proprietary medicinal product is an addition to the range which does not provide an improvement in actual benefit (IAB V).
Studies requested	-

Assessment of OXYNORMORO proprietary medicinal products prior to the change in the marketing authorisation wording of 9 July 2010

Date of opinion (reason for the request)	6 February 2008 NHI/ Hospital Use listing of 5, 10 and 20 mg orodispersible tablets.
Indication	Chronic cancer-related pain, severe or unresponsive to weaker analgesics, in adults (from 18 years)
AB	Substantial
IAB	These proprietary medicinal products are additions to the range and do not provide an improvement in actual benefit.
Studies requested	-

Assessment of the proprietary medicinal products OXYCONTIN PR, OXYNORM and OXYNORMORO after the change in the marketing authorisation wording of 9 July 2010

Date of opinion (reason for the request)	19 September 2012 (renewal of inclusion and extension of indication)
Indication	Treatment of severe pain which can be adequately managed only with strong opioid analgesics, in particular cancer pain
AB	The actual benefit of these proprietary medicinal products remains substantial in the treatment of severe, cancer pain in adults which can be adequately managed only with strong opioid analgesics. In severe acute pain (postoperative pain), the actual benefit of these proprietary medicinal products is substantial. In severe chronic pain: neuropathic pain, the actual benefit of these proprietary medicinal products is substantial. In severe chronic rheumatic pain: osteoarthritis, lumbar and neck pain, etc. the actual benefit of these proprietary medicinal products is insufficient relative to existing therapies, to justify their reimbursement by national health insurance in this type of pain.
IAB	The proprietary medicinal products OXYCONTIN, OXYNORM and OXYNORMORO do not provide any improvement in actual benefit (IAB V) relative to immediate and prolonged-release morphine-based proprietary medicinal products in the management of severe cancer, postoperative and neuropathic pain.

Studies requested	-

07.1 International information on the medicinal product

Oxycodone-based proprietary medicinal products are reimbursed in all of the countries of the European Union.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company has provided 2 Cochrane reviews and a literature review of the evaluation of the efficacy of opioids in chronic lumbar pain or pain from hip and knee osteoarthritis:

One Cochrane review (Chaparro et al, 2013)[3] of the evaluation of the efficacy of opioids in chronic lumbar pain included 15 studies (or 5540 patients) including 6 studies with strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, tapentadol). The duration of the studies was between 4 and 16 weeks. The authors retained only a single study (Webster, 2006)[4] with oxycodone in combination with naltrexone, an opiate-inhibitor (not described in this opinion). This meta-analysis concludes that there is evidence for the short-term efficacy of strong opioids, but only of low to medium quality, both on pain intensity and function, compared with placebo. Regarding safety, these studies do not report serious reactions or complications (overdose, addiction) but the rate of study drop-outs is high (25 to 30%).

A Cochrane review (Nüesch et al, 2009)[5] evaluated oral opioids (codeine, oxycodone, oxymorphone, morphine) or transdermal opioids (fentanyl) in osteoarthritis of the hip and knee. This review included 10 studies (or 2268 patients) but only 4 studies with oxycodone. It concluded that the benefits of using oral opioids (codeine, oxycodone, oxymorphone, morphine) or transdermal opioids (fentanyl) in osteoarthritis of the hip and knee were at best moderate in view of adverse events. However, the authors recommend limiting their use in these diseases.

A clinical literature review[6] (Avouac, 2007) aimed to determine the analgesic efficacy, effect on physical functioning and safety of opioids in patients with osteoarthritis. Eighteen randomised, placebo-controlled trials were included with information on pain severity available for 13 trials, corresponding to 2438 patients treated with an analgesic and 1295 treated with placebo. Six studies evaluated strong opioids (oxycodone (4), fentanyl (1) and morphine sulfate (1)). Overall, the mean duration of the trials was 13 ± 18 weeks (median: 12 weeks, [1.4-72 weeks]). The efficacy of treatment was evaluated in terms of pain relief (0-100 mm VAS, WOMAC OA index and 4-point or 5-point Likert scale) and functional improvement (WOMAC). Opioids reduced the severity of osteoarthritis pain with a functional benefit judged to be modest compared with placebo (-0.31 (95% CI -0.39 to -0.24 with consistent results and a pooled effect of strong opioids on pain severity: -0.79 (95% CI -0.98 to -0.59) with substantial heterogeneity (Q=198.5, p<0.0001).

[3] Chaparro LE et al. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database of Systematic Reviews 2013, Issue 8, Art n° D004959.DOI:10.1002/14651858.CD004959.pub4

[4] Webster LR et al. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in lumbar pain. Journal of Pain 2006;7:937-46.

[5] Nüesch E. et al, Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2009, Issue 4, Art. No.: CD003115.DOI:10.1002/14651858.CD003115.pub3.

[6] Avouac J et al. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. OsteoArthritis and Cartilage 2007;15: 957-65.

The company also provided 5 clinical studies:

- 3 studies in osteoarthritis: Markenson (2005),[7] Roth (2000),[8] Caldwell (1999),[9]
- 3 studies in lumbar pain: Hale (1999)[10] and 2 unpublished studies from the marketing authorisation dossier (OC961002 conducted from January 1998 to May 1999, OXCOCLIN0014 conducted from June 1999 to August 2001),
- 1 study in acute exacerbations of chronic neck pain: Ma (2008)[11]

These clinical studies were all analysed by the Transparency Committee in its opinion of 19 September 2012.

08.2 Adverse effects

8.2.1 Data from studies

The company did not provide new data relative to those already assessed in the Transparency Committee opinion of 19 September 2012 ((Ytterberg (1998),[12] Portenoy (2007)[13]).

8.2.2 PSUR data

The latest summary documents (PSURs) sent to the ANSM include data recorded internationally from 13 April 2011 to 12 April 2012.
In the period from 13 October 2011 to 12 April 2012, it was shown that the most important issue was abuse, dependence and overdoses, these being almost exclusively encountered in the United States and the subject of national monitoring by the CEIP [Centre for Evaluation and Information on Pharmacodependence] in France (see section 8.2.3 Data from ANSM monitoring).

8.2.3 Data from ANSM monitoring

In France, oxycodone has been subject to special monitoring since being put on the market.
During the meeting of 24 October 2013 of the Commission nationale des stupéfiants et des psychotropes [French National Narcotics and Psychotropic Drugs Commission], the CEIP of Toulouse presented an update on abuse, dependence and misuse with oxycodone in France.[14] This assessment, relating to the period from 2008 to June 2013 states that “The exposure data show an increase in oxycodone consumption, probably related to the extension of indication to non-cancer pain in 2010 and to an improvement in pain management. This increased exposure is accompanied by an increase in notifications in the various tools of the addictovigilance network. In the majority of cases, abuse or dependence results from treatment of pain with oxycodone.

[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: 524:35.
[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 ;160:853-60.
[9] Caldwell JR et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26:862-9.
[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;15:179-83.
[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; 62: 241-7. Epub 2007 Dec 6.
[12] Ytterberg SR et al. Codeine and oxycodone use in patients with chronic rheumatic disease pain. Arthritis Rheum 1998;41:1603-12.
[13] 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;23:287-99.
[14] ANSM. Comité technique des Centres d’Evaluation et d’Information de la Pharmacodépendance [Technical Committee of the Centres for Evaluation and Information on Pharmacodependence] -CT022013033. Compte rendu de séance du 24 octobre 2013 [Minutes of the meeting of 24 October 2013].

The use of oxycodone appears to be becoming more common and it is necessary to remember that, like any step 3 opioid analgesic such as morphine and fentanyl, its potential for abuse and primary dependence is substantial.
Furthermore, preliminary cases of doctor shopping, intravenous administration and misuse have been recently reported.
In this context, surveillance of the use of oxycodone in France should be continued and the ANSM wishes to remind prescribers of the risk related to its use".
The ANSM also states that[15] "addictovigilance shows that, unlike what is observed in the United States, the misuse of oxycodone in France is limited due to a suitable framework for its prescribing and dispensing conditions that does not reduce access to treatment".

08.3 Other data

8.3.1 Prescription data

In a sample of 16,812 prescriptions from general practitioners, the distribution of step 3 opioid prescriptions is as follows:

Product	Number of prescriptions	% of prescriptions
Morphine PR	3,957	23.5
Morphine IR	2,718	16.2
Oxycodone PR	3,401	20.2
Oxycodone IR	2,232	13.3
Fentanyl PR	3,709	22.1
Fentanyl IR	652	3.9

(Source: IMS, Disease Analyzer database 2013 data)

The proportion of patients treated with oxycodone in a rheumatic context represented 59% of prescriptions. The longitudinal Disease Analyzer database only documents prescriptions by general practitioners and does not provide information on initial hospital prescriptions or prescriptions issued by specialists.
Extrapolating from these data allows estimation of the population of patients with an oxycodone prescription issued by a general practitioner at 53,700 in 2013. Estimating from prescriptions by general practitioners or private or hospital specialists, dispensed in retail pharmacies gave a number of patients treated of around 131,000 patients (source: IMS Lifelink Treatment Dynamics).
The mean daily dosage of oxycodone prescribed during the year 2013 was 33.5 mg, with a median of 20 mg (min. 5 mg; max. 480 mg).
For rheumatic pain, the mean daily dosage observed is 30.1 mg; less than that for cancer pain at 43.4 mg.
The mean treatment duration was 67 days, with a median of 28 days (min. 2 days; max. 448 days).
There was no evidence of a notable difference in treatment durations according to indications.

The reasons for prescribing oxycodone for rheumatic issues from the IMS data (as a moving annual total (MAT) August 2014) are given in the table below.

Proprietary medicinal product	Number of prescriptions all indications combined	Number of prescriptions in rheumatology

[15] ANSM. Oxycodone (Oxycontin, Oxynorm, Oxynormoro): risque d'abus et de pharmacodépendance équivalent à celui des autres antalgiques opiacés de palier III [risk of abuse and drug dependence equivalent to that of other step 3 opiate analgesics]. Vigilances number 61 April 2014.

	(MAT August 2014)	(MAT August 2014)
OXYCONTIN PR OXYNORM OXYNORMORO	478,620	Lumbar pain: 28,841 Sciatica: 28,691 Osteoarthritis: 23,732 Lumbago with sciatica: 17,190 Hip osteoarthritis: 10,288 Rheumatoid arthritis: 9,832 Cervicobrachial syndrome: 8,358 Osteoporosis: 5,803 Compression fracture: 5,631 Back pain: 4,922 Polyarthritis: 3,558 Ankylosing spondylitis: 2,576 Other spondylarthrosis: 2,317 Osteoporosis with pathological fracture: 2,317 Rheumatism: 1,077

09 SUMMARY & DISCUSSION

In its opinion of 19 September 2012, in the context of extension of indications for oxycodone-based proprietary medicinal products in non-cancer pain, the Committee stated that:
"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 postoperative 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 suggest 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 lumbar pain, the available data (including a negative study versus placebo) did not demonstrate the efficacy of oxycodone in controlling pain 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 on the 7th day for the two endpoints.

For oxycodone, as with all narcotics, there is a risk of dependence 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 clinical studies which do not formally show its clinical benefit, its adverse effects and the risk of dependence."

Since this assessment, no new efficacy or safety clinical study data have been identified with oxycodone. Cochrane reviews or literature reviews to evaluate strong opioids, including oxycodone, in chronic non-cancer and non-neuropathic pain confirm the modest efficacy of strong opioids, including oxycodone, in chronic osteoarthritis and lumbar pain and the lack of data with a high level of evidence on efficacy and safety, especially in connection with long-term use.

The safety profile of oxycodone has not changed. In France, misuse of oxycodone, whose use in all indications combined is increasing, appears limited, unlike the United States.14,[16]
According to an analysis of 16,812 prescriptions from a panel made up solely of general practitioners, 59% of oxycodone prescriptions were issued for rheumatic indications (Source: IMS, Disease Analyzer database 2013 data). Despite the lack of clinical efficacy and safety data of acceptable methodological quality, many French and foreign guidelines recommend the use of strong opioids in chronic rheumatic pain, with certain conditions or restrictions and with strict supervision (see section 10 Therapeutic use).

010 THERAPEUTIC USE

In chronic non-cancer pain:
Chronic non-cancer pain is a complex and multifactorial syndrome that is considerably influenced by psychological, social and environmental factors. The management of this type of pain is multimodal, including treatment of the causal disease, analgesic pharmacological and non-pharmacological treatments and treatment of psychological, social and professional aspects.[17]

In 2004, AFSSAPS2 stated that "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 must be ensured that the somatic cause is clearly identified, that the pain is intense, not sufficiently controlled by etiologic treatments and that "standard" analgesic treatments (other than strong opioids) are ineffective when they are correctly prescribed and evaluated."
Opioid treatment should form part of a comprehensive management approach drawing upon other pharmacological and non-pharmacological treatments (psychotherapy, physiotherapy and rehabilitation).
Strong opioids for CNCRP should be prescribed within the context of a "Contract of objectives and means": "Treatment will only be started after information has been given by the doctor and accepted by the patient concerning the aims of treatment and the conditions and methods of prescribing, follow-up and any discontinuation of treatment. This approach requires everyone to adhere to a code of conduct allowing controlled use of the medicine."

Six key points
1. the **management** of CNCRP is **comprehensive**: the patient's complaint must be evaluated by considering somatic, psychological and socio-professional factors;
2. The WHO pain ladder strategy for using analgesics in cancer pain does not apply to all chronic pain syndromes;
3. Using strong opioids in CNCRP is a **second-line treatment**;
4. Some chronic pain syndromes have little sensitivity to opioids and opioids are not indicated in these conditions, particularly where the pathophysiological mechanism has not been clearly established;
5. If there is any doubt as to indication, a specialist opinion should be sought from a clinician working in a pain management facility;
6. The **risks of using** strong opioids must be taken into account:
- the occurrence of adverse effects: primarily gastrointestinal disorders (nausea and vomiting at the start of treatment; constipation which often requires use of a laxative throughout the duration of treatment), confusion, sedation, dysphoric effects, impaired cough reflex and respiratory depression. Clinicians should be especially vigilant in very elderly patients.

[16] Franklin GM. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. Neurology 2014; 83; 1277-1284.
[17] Bertin P, et al. Opioïdes forts et douleurs chroniques non cancéreuses rhumatologiques [Strong opioids and chronic non-cancer rheumatic pain]. Médecine. January 2008.

- the possibility of inducing physical and/or psychological dependence or drug tolerance;
- during long term use: possible occurrence of endocrine disruption, impaired immune response or possible genetic changes related to potential genotoxic properties.

AFSSAPS has formulated a reference principle: "At the end of a **test period**, the risk/benefit ratio of using a strong opioid is considered to be favourable if the analgesic effect is judged to be significant and any adverse effects are judged to be minor by the patient and the doctor, without any associated effects such as abuse or dependence."

"The choice of **dosage form** is determined by the circadian rhythm of the pain, any triggering factors or the existence of intercurrent acute episodes of pain. Thus:
- In severe and constant pain occurring on a daily basis, a prolonged-release (PR) form is recommended.
- Severe but intermittent pain may justify use of an immediate-release (IR) form.
In chronic non-cancer pain, parenteral administration in an outpatient department should be disallowed unless use of an oral form is impossible.

In 2008, the increasing use of strong opioids in chronic non-cancer pain remained controversial due to the lack of published studies confirming their efficacy, their adverse effects, and concerns regarding drug tolerance and dependence.18

In 1999, the Limoges guidelines[18] aimed to evaluate the scientific data available and to set out recommendations for using morphine, at the time the only opioid to have an indication compatible with the treatment of non-cancer rheumatic pain. This preliminary work was **updated in 2010**.[19] In these more recent guidelines, strong opioids – which, according to the authors, are increasingly prescribed in chronic non-cancer pain – are recommended under certain conditions.
Strong opioids should not be considered as a first-line treatment.
There are insufficient clinical data to recommend using one strong opioid over another. Nonetheless, the oral and prolonged-release forms are preferred in the first instance.

According to the Limoges guidelines, in hip and knee osteoarthritis, strong opioids may be proposed after failure or insufficient action of the usual recommended treatments, or if there is a contraindication to surgery, or while awaiting surgery. It is preferable to use strong opioids with prolonged release to act on pain, and, to a lesser degree, function.

The 2003 EULAR[20] (European League Against Rheumatism) recommendations for osteoarthritis of the knee and the 2005 EULAR[21] recommendations for osteoarthritis of the hip mention the use of opioids (without specifying whether strong or weak) after paracetamol and NSAIDs have failed (inefficacy, intolerance) or where they are contraindicated.

[18] Perrot S et al. Utilisation de la morphine dans les douleurs rhumatologiques non cancéreuses: les recommandations de Limoges. [Use of morphine in non-cancer rheumatic pain: Limoges guidelines]. Rev Rhum 1999; 66: 651-657.
[19] Vergne-Salle P et al. Les opioïdes forts dans les douleurs ostéo-articulaires non cancéreuses : revue de la littérature et recommandations pour la pratique clinique [Strong opioids in non-cancer bone and joint pain: literature review and guidelines for clinical practice]: « les recommandations de Limoges [Limoges guidelines] 2010 ». Douleurs Evaluation – Diagnostic – Traitement [Pain Assessment – Diagnosis – Treatment]. 2012; 13: 259-275.
[20] Jordan KM, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62: 1145-55.
[21] Zhang W, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005; 64: 669-81.

The 2009 OARSI[22] (Osteoarthritis Research Society International) recommendations recommend using strong opioids in severe pain under exceptional circumstances. Non-pharmacological treatments should be pursued and surgery should be considered.
The 2012 ACR[23] (American College of Rheumatology) recommendations are specific when it comes to osteoarthritis of the hands: they do not recommend opioids. In osteoarthritis of the knee and hip, they recommend opioids for symptomatic patients who have not responded adequately to other pharmacological agents and non-pharmacological treatments and who are not candidates for surgery.

According to the latest Limoges guidelines, in chronic neck pain, prescribing strong opioids is only considered in select patients: after failure of conventional pharmacological and non-pharmacological treatments and in cases where psychological and/or socio-professional components do not override their use.

In rheumatoid arthritis, strong opioids may be used in the long or short term for pain that is resistant to other analgesic therapies, anti-inflammatories and disease-modifying drugs including biological agents.

In chronic pain from osteoporotic vertebral fractures, strong opioids may be offered if the treatments usually recommended for this condition have failed or are insufficient, to ease patients' symptoms and restore independence.

In chronic lumbar pain, prescribing strong opioids is only considered in select patients: after failure of conventional pharmacological and non-pharmacological treatments and in cases where psychological and/or socio-professional components do not override their use, with the aim of improving function, to help set up a rehabilitation programme and in patients who are re-assessed very regularly.

In this disease, **in December 2000**, the **ANAES**[24] [National Health Accreditation and Assessment Agency] guidelines on the diagnosis, management and follow-up of patients with chronic lumbar pain authorised the use of step 3 opioids under the following limited conditions: "The use of step 3 analgesics (strong opioids) in chronic lumbar pain may be considered on a case-by-case basis and complying with contraindications (grade C). This type of treatment is intended for patients in whom other therapeutic approaches have failed, in particular where step 1 and 2 analgesics have failed and after depression has been ruled out. Follow-up should include a pain assessment and screening for adverse effects. The duration of treatment should be limited and it should be stopped gradually (professional consensus)."

In Belgium, in its 2006 guidelines on **chronic lumbar pain,**[25] the Centre fédéral d'expertise des soins de santé [Belgian Healthcare Knowledge Centre], which is responsible for conducting studies to clarify policy decisions in the areas of healthcare and national health insurance under the auspices of the Minister for Public Health and Social Affairs, stated that the quality of evidence in the efficacy data for opioids in chronic lumbar pain was poor (based on the Maier et al. study)[26] and that they have substantial potential adverse effects, including addiction.

[22] Henrotin Y, et al. French translation of the Osteoarthritis Research Society International (OARSI) recommendations for the management of knee and hip osteoarthritis. Revue du rhumatisme 2009; 76: 279-88.
[23] American College of Rheumatology. Recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. 2012.
[24] Agence Nationale d'Accréditation et d'Evaluation en Santé, ANAES. Diagnostic, prise en charge et suivi des malades atteints de lombalgie chronique. [Diagnosis, management and follow-up of chronic lumbar pain patients]. December 2000.
[25] Centre fédéral d'expertise des soins de santé [Belgian Health Knowledge Centre]. Lombalgie chronique [Chronic lumbar pain]. KCE reports vol. 48B.2006.
[26] Maier C. et al. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain results of a double-blind controlled trial (MONTAS). Pain 2002; 97: 223-33.

In 2007, the American College of Physicians (ACP) and the American Pain Society published joint guidelines on the diagnosis and management of lumbar pain.[27]
In the majority of patients, the use of paracetamol or an NSAID is recommended as a first-line therapy, after the clinician has assessed the patient's pain severity, functional impairment and risk profile. Opioids and tramadol are an alternative in severe acute or chronic lumbar pain and where the pain leads to disability that is not controlled by paracetamol or NSAIDs. The potential benefits and risks should be carefully assessed by the physician (particularly as concerns the risks of abuse and dependence). In the case of chronic pain, tricyclic antidepressants may also be an alternative.

In the United Kingdom, in 2009, the NICE guidelines[28] authorised the use of strong opioids for the short-term treatment of severe pain; treatment may be continued after a specialist has re-assessed the efficacy/adverse effects ratio; tricyclic antidepressants are considered as an alternative.

In Canada, in the absence of data, the guidelines[29,30] do not recommend using strong opioids such as oxycodone or morphine in lumbar pain or fibromyalgia.

✓ **European, American and Canadian guidelines for chronic non-cancer pain**

The American ASIPP guidelines (2012)[31] conclude that the evidence for the long-term efficacy of opioids is not convincing due to the relatively short duration of studies (3 months). The guidelines drawn up by the ASIPP are based more on practices than on demonstrations of good methodological quality.
The ASIPP (2012)[32] and American Pain Society (APS, 2009)[33] guidelines on using opioids in chronic non-cancer pain recommend carrying out a complete assessment of the patient before starting long-term treatment with a strong opioid, including an examination of the history and clinical parameters and appropriate tests particularly for the detection of any drug dependence, misuse or addiction. Similarly, the risk/benefit ratio should be carefully assessed before starting strong opioids, and then at regular intervals during treatment. In general, opioids in non-cancer pain should be reserved for select patients in whom long-term treatment with a strong opioid can be considered to manage moderate to severe pain which has an adverse impact on the patient's functional capacity or quality of life, as long as the expected benefits outweigh the potential risks.

The recommendations in the Canadian guidelines[29,30] are similar. Opioids should be reserved for patients with defined physical or neuropathic pain that has not responded to non-opioid treatment.

In the United Kingdom, the British Pain Society has published good practice guidelines for using opioids in chronic pain.[34] The learned society confirms that there is a lack of data on long-term analgesic efficacy. Complete pain relief is rarely obtained with opioids. The aim of treatment is to reduce symptoms in order to improve functional capacity. Before treatment is started, patients

[27] Chou R, et al. Diagnosis and treatment of lumbar pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med 2007; 147: 478-91.
[28] National Institute for Health and Clinical Excellence. Low back pain; early management of persistent non-specific low back pain. May 2009.
[29] Kahan M, et al. National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. Can Fam Physician 2011; 57: 1257-66, e407-18.
[30] Kahan M, et al. National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. Can Fam Physician 2011; 57: 1269-76, e419-28.
[31] Manchikanti L, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I-Evidence assessment. Pain Physician 2012; 15:S1-S66.
[32] Manchikanti L, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2-Guidance. Pain Physician 2012; 15:S67-S116.
[33] Chou R, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain 2009; 10: 113-30.
[34] The British Pain Society's. Opioids for persistent pain: good practice. January 2010.

must be informed of adverse events (80% of patients on opioids will experience at least one adverse event). Patients should be informed that little is known about the long-term effects on endocrine and immune function.

In 2013, Freynhagen and other German authors[35] noted the lack of methodologically correct data supporting the use of strong opioids in non-cancer pain for a duration of more than 6 weeks. However, the authors make recommendations on the use of strong opioids in non-cancer pain in terms of precautions to take before prescribing, patient information, managing adverse events and monitoring treatment.

In Switzerland, the 2005 recommendations for using opioids in chronic pain[36] attempt to set rules facilitating the prescription of opioids by making doctors aware of the factors involved in safe use of these substances. It is very important that opioid treatment is prescribed within the context of a comprehensive therapeutic management approach. This publication sets out detailed rules on required conditions, onset, duration, risk prevention in long-term treatment and how to stop opioid treatment. It emphasises the importance of understanding the safety profile and the potential for interaction before considering prescribing an opioid.

In conclusion, in view of these different French and foreign guidelines on the use of strong opioids in chronic non-cancer and non-neuropathic pain, which make the following points in particular:

- the use of strong opioids should only be considered after the standard drug and non-drug therapies recommended in these indications have failed;
- in non-cancer pain, strong opioids should be restricted to select patients;
- long-term treatment with a strong opioid can be considered to manage pain which has an adverse impact on the patient's functional capacity or quality of life, as long as the expected benefits outweigh the potential risks;
- a complete assessment of the patient should be carried out before starting long-term treatment with a strong opioid, including an examination of the history and clinical parameters and appropriate tests particularly for the detection of any drug dependence, misuse or addiction;
- the risk/benefit ratio should be carefully assessed before starting strong opioids, and then at regular intervals during treatment;

In intractable chronic pain caused by mechanical disorders, primarily osteoarthritis and chronic lumbar pain:

✓ **In osteoarthritis of the lower limbs**, a condition for which there is currently no disease-modifying treatment, pharmacological and non-pharmacological approaches should be used.
The first steps to take are diet and lifestyle based (losing excess weight, regular physical activity except during flare-ups of pain or congestion where reduced activity is necessary) and non-pharmacological (physical therapy, wearing orthotics, using sticks, etc.).
During symptomatic phases, the 1st-line pharmacological treatment is paracetamol. During acute episodes, short courses of oral NSAIDs at the lowest effective dose in patients who do not respond to paracetamol. Topical NSAIDs may be an alternative to oral NSAIDs.
Local analgesic treatments, especially topical NSAIDS and intra-articular corticosteroid injections, can also be used especially during congestive phases.

Medicines such as chondroitin sulfate, unsaponifiable components of avocado and soybean oil, diacerein and glucosamine have minimal effects on pain and functional disability. It has not been

[35] Freynhagen R. et al. Opioids for chronic non-cancer pain. BMJ 2013 29; 346.
[36] Aeschlimann A. et al. Recommandations pour l'usage des opioïdes lors de douleurs chroniques [Recommendations for the use of opioids in chronic pain]. 1re partie [part 1]. Schweiz Med Forum 2005; 5: 1203–1209.

demonstrated that they reduce NSAID consumption, which causes very notable and often serious adverse effects, in particular in the elderly. Consequently, they have no role in the therapeutic strategy.
Weak opioids may be used when other treatments have failed.
Surgery (arthroplasty, prosthetic implant) is reserved for radiologically advanced osteoarthritis that is painful and disabling and resistant to the usual therapeutic measures.
Strong opioids may be considered as a last-resort treatment for osteoarthritis of the hip or knee, in case of intense and/or intractable pain episodes, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery, for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. This therapeutic category should be used as little as possible, after the failure of other recommended pharmacological and non-pharmacological measures (including physiotherapy); Use of an oral form is preferred.

✓ In the absence of clinical data, strong opioids have no role in the therapeutic management of **osteoarthritis of the fingers**.

✓ **In chronic lumbar pain**, pharmacological and non-pharmacological treatments should be considered in the first instance together with physical measures, particularly physiotherapy- and pharmacology-based approaches: paracetamol for the first-line and then NSAIDs. A weak opioid may also be considered for refractory pain.
Strong opioids may be considered as a last-resort treatment in chronic lumbar pain, in case of intense and/or intractable pain flares and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. This therapeutic category should be used as little as possible, after failure of other recommended pharmacological and non-pharmacological measures (including physiotherapy); Use of an oral form is preferred.

With the exception of severe intractable pain in mechanical rheumatic diseases such as osteoarthritis of the knee or hip and chronic lumbar pain and under the conditions specified above, strong opioids have no role in the therapeutic strategy for chronic non-cancer and non-neuropathic pain, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis. A Cochrane Review[37] (Whittle SL et al, 2011) assessing opioids in rheumatoid arthritis pain included 11 studies of which only one was a randomised, crossover study with morphine (Moran 1991) with a duration of no more than 6 weeks. In this study, half of the patients withdrew due to inefficacy or intolerance during the morphine phase.
1st-line symptomatic treatments, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, are effective at improving inflammatory flare-ups of spondyloarthritis (NSAIDs) or rheumatoid arthritis (corticosteroids). Standard disease-modifying drugs and biological agents have transformed the prognosis of these diseases.

The role of oxycodone-based proprietary medicinal products in chronic non-cancer and non-neuropathic pain
Oxycodone, as a strong opioid, has a role in the therapeutic strategy for pain episodes encountered in the context of mechanical rheumatic disease such as knee or hip osteoarthritis and chronic lumbar pain and under the conditions specified above.
The decision to prescribe oxycodone, as for other strong opioids, must be made in consideration of its safety profile[38] and the potential for misuse or abuse.

[37] Whittle SL et al. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database of Systematic Reviews 2011, Issue 11, Art. No.: CD003113.DOI:10.1002/14651858.CD003113.pub3.
[38] According to the SPC, the most common adverse effects at the usual doses are: constipation, drowsiness, confusion, nausea and vomiting.

Oxycodone has no role in the therapeutic strategy for management of chronic non-cancer and non-neuropathic pain, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

010.1 Target population

Taking into account their therapeutic use as a last-resort treatment in severe intractable pain episodes in osteoarthritis of the knee or hip and chronic lumbar pain, after other pharmacological treatments and physiotherapy have failed, a very small proportion of patients with osteoarthritis or lumbar pain are eligible for strong opioid treatment.
No data were identified that could be used to precisely estimate the population with osteoarthritis or lumbar pain eligible for treatment with strong opioids.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

011.1 Actual benefit

◗ Chronic (defined by a duration greater than 3 months) non-cancer and non-neuropathic pain is essentially rheumatic. Although it generally consists of moderate pain, it can sometimes be severe pain that has a major impact on patients' quality of life, or even leads to genuine disability. It may also have a psychological impact, particularly when it is severe and/or chronic, triggering anxiety or depression.

◗ Oxycodone-based proprietary medicinal products are a symptomatic treatment.

◗ The efficacy/adverse effects ratio of oxycodone-based proprietary medicinal products is modest.

◗ There are pharmacological treatment alternatives at this stage of the disease (other strong opioids) and non-pharmacological alternatives (surgery).

◗ Oxycodone-based proprietary medicinal products may be considered as a last-resort treatment in osteoarthritis of the hip or knee, in case of severe intractable pain episodes, at a stage where surgery is planned and in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery, for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. These medicinal products should be used as little as possible, after the failure of other recommended pharmacological and non-pharmacological treatments (including physiotherapy).
Oxycodone-based medicinal products may be considered as a last-resort treatment in chronic lumbar pain, in case of severe intractable pain episodes and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. These medicinal products should be used as little as possible, after the failure of other recommended pharmacological and non-pharmacological treatments (including physiotherapy).
In all cases, the use of an oral form is preferred. The decision to prescribe oxycodone, as for other strong opioids, must be made in consideration of its safety profile38 and the potential for misuse or abuse.
In the absence of clinical data, oxycodone-based proprietary medicinal products have no role in the therapeutic management of osteoarthritis of the fingers.
With the exception of severe intractable pain in mechanical rheumatic diseases like osteoarthritis of the knee or hip and chronic lumbar pain and under the conditions specified above, oxycodone-based proprietary medicinal products have no role in the therapeutic strategy for chronic non-cancer and non-neuropathic pain, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

Consequently, the Committee considers that the actual benefit of the proprietary medicinal products OXYCONTIN PR, OXYNORM, OXYNORMORO is:
- substantial in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term efficacy and safety data. Oxycodone-based medicinal products should be used as little as possible, after the failure of other pharmacological and non-pharmacological treatments (including physiotherapy) recommended in these indications;

- <u>insufficient</u> in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

APPENDIX

✓ **Morphine-based comparators in prolonged-release oral forms**

NAME (INN) Company	Indications	Date of TC Opinion	Actual Benefit	Reimbursed Yes/No
SKENAN PR (Morphine sulfate) *Bristol-Myers Squibb*	Persistent intense pain or pain resistant to other analgesics, particularly cancer pain.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned and in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes
MOSCONTIN MOSCONTIN PR (Morphine sulfate) *Mundipharma*	Persistent intense pain or pain resistant to weaker analgesics, especially cancer-related pain.	19/03/2014		Yes

✓ **Morphine-based comparators in immediate-release oral forms**

NAME (INN)	Indications	Date of TC Opinion	Actual Benefit	Reimbursed Yes/No
ACTISKENAN (Morphine sulfate) *Bristol-Myers Squibb*	Intense pain or pain resistant to weaker analgesics, especially cancer-related pain.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes
SEVREDOL (Morphine sulfate) *Mundipharma*	Intense pain or pain resistant to weaker analgesics, especially cancer-related pain.	19/03/2014		Yes
ORAMORPH (Morphine sulfate) *Norgine Pharma*	Intense pain or pain resistant to weaker analgesics, especially cancer-related pain.	19/03/2014		Yes

✓ **Morphine-based comparators for injection**

NAME (INN)	Indications	Date of TC Opinion	Actual Benefit	Reimbursed Yes/No
MORPHINE LAVOISIER (Morphine sulfate) *CDM Lavoisier*	1 mg/ml Intense pain and/or pain resistant to weaker analgesics. 50 mg/ml Intense pain and/or pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes
MORPHINE AGUETTANT (morphine hydrochloride) *Aguettant*	0.1, 1, 10, 20 mg/ml Intense pain and/or pain resistant to weaker analgesics. 40 mg/ml Intense pain and/or pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	19/03/2014		Yes
MORPHINE LAVOISIER (morphine hydrochloride) CDM Lavoisier	10, 20 mg/ml Intense pain and/or pain resistant to weaker analgesics.	19/03/2014		Yes
MORPHINE RENAUDIN (morphine hydrochloride) *Renaudin*	1, 10, 20 mg/ml Intense pain and/or pain resistant to weaker analgesics. 40 mg/ml Intense pain and/or pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	19/03/2014		Yes
MORPHINE COOPER (morphine hydrochloride) *Cooperation pharmaceutique francaise*	10 mg/ml Intense pain and/or pain resistant to weaker analgesics.	19/03/2014		Yes

✓ **Immediate or prolonged-release comparators based on other strong opioids:**

NAME (INN)	Indications	Date of TC Opinion	Actual Benefit	Reimbursed Yes/No
DUROGESIC and its generics (Fentanyl) *Janssen-Cilag*	Treatment of severe, chronic pain which can be adequately managed only with strong opioid analgesics.	15/12/2010	**Insufficient** in non-cancer pain given the results observed in studies filed in lumbar pain and osteoarthritis in terms of efficacy and safety and the absence of data in other non-cancer pain models.	Yes
MATRIFEN (similar to DUROGESIC) (Fentanyl) *Takeda*	Transdermal treatment of intense chronic pain, as a replacement for strong opioids, after their efficacy has been established.	10/12/2008		Yes
TEMGESIC (Buprenorphine) *RB Pharmaceuticals*	Intense pain, particularly postoperative pain and tumour pain.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes

PETHIDINE RENAUDIN (Pethidine) *Renaudin*	Intense pain and/or pain resistant to weaker analgesics.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes
NALBUPHINE AGUETTANT (Nalbuphine) *Aguettant*	Intense pain and/or pain resistant to weaker analgesics.	19/03/2014	**Substantial** in the management of intense and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic lumbar pain, as a last-resort treatment, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery (in osteoarthritis of the hip or knee), and for the shortest duration possible due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as little as possible, after the other pharmacological treatments and physiotherapy recommended in these indications have failed. **Insufficient** in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, especially in chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.	Yes
NALBUPHINE MYLAN (Nalbuphine) *Mylan*				Yes
NALBUPHINE SERB (Nalbuphine) *Serb*				Yes
PALEXIA LP (Tapentadol) *Grunenthal*	Treatment of severe, chronic pain in adults which can be adequately managed only with opioid analgesics.	25/06/2014	**Insufficient** in the treatment of severe, chronic non-cancer pain in adults which can be adequately managed only with opioid analgesics.	No
TARGINACT (Oxycodone + naloxone) *Mundipharma*	Intense pain which can be adequately managed only with opioid analgesics. Naloxone, an opioid antagonist, is added to neutralise the constipation induced by the opioid by locally inhibiting the action of oxycodone in the intestinal receptors.	07/12/2011	**Insufficient** in severe non-cancer pain	No