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TRANSPARENCY COMMITTEE
Opinion
19 March 2014

NALBUPHINE SERB 20 mg/2 ml, solution for injection

B/10 (CIP: 34009 368 941 0 5)

B/5 (CIP: 34009 358 318 9 7)

Applicant: SERB

INN	nalbuphine
ATC code (2013)	N02AF02 (morphinan derivatives)
Reason for the review	Re-assessment of the Actual Benefit of strong opioids indicated in chronic non-cancer and non-neuropathic pains at the Committee's request, in compliance with article R-163-21 of the French Social Security Code
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication concerned	Indications concerned by the re-assessment: Chronic non-cancer and non-neuropathic pains

Actual Benefit	The actual benefit of the proprietary medicinal product NALBUPHINE SERB 20 mg/2 ml, solution for injection is: - substantial in the management of severe and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic low back 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 possible duration due to the risk of serious adverse effects and the absence of long-term data. This therapeutic category should be used as limited 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, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.
Therapeutic use	Strong opioids may be considered as a last-resort treatment in osteoarthritis of the hip or knee, in case of severe intractable pain, 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 possible duration 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 recommended pharmacological treatments and physiotherapy have failed. 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. Strong opioids may be considered as a last-resort treatment in chronic low back pain, in case of severe intractable pain and for the shortest possible duration 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 recommended pharmacological treatments and physiotherapy have failed. Use of an oral form is preferred. With the exception of severe intractable pain in the mechanical rheumatic diseases 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.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date of Marketing Authorisation (national procedure): B/5: 14 December 2001 B/10: 7 May 2004
Prescribing and dispensing conditions/special status	List I.

TRANSPARENCY COMMITTEE

Assessment Report

19 March 2014

02 BACKGROUND AND PURPOSE OF THE RE-ASSESSMENT

The Transparency Committee (TC) of HAS assesses medicinal products that have obtained Marketing Authorisation (MA) when the company marketing them wishes them to be included on the list of refundable medicines (articles L.162-17 of the French Social Security Code and L.5123-2 of the French Public Health Code) or on request.

The TC is a scientific body comprised of physicians, pharmacists and specialists in methodology and epidemiology.

Its objective are:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospitals, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer over treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant, independent scientific information on the products.

These objectives are defined in the French Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.

According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76 and R. 161-85 of the French Social Security Code and articles L. 5123-2 and L. 5123-3 of the French Public Health Code, the opinions of the TC specify the actual benefit and improvement in actual benefit provided by the medicinal products.

This assessment is performed on the basis of a critical analysis of the scientific data available using evidence-based medicine and experts opinion, in accordance with the indications and dosages in the Marketing Authorisation.

02.1 History and background of the re-assessment

While re-assessing a proprietary medicinal product part of the strong opioid class, as there were questions relating to efficacy in non-cancer and non-neuropathic pain, the Transparency Committee decided to re-assess the actual benefit of the strong opioids indicated in **chronic non-cancer and non-neuropathic pain** where no specific opinion has been delivered in these indications.

The scope of indications concerned particularly includes rheumatic pain in the context of low back pain and osteoarthritis. Moderate to severe post-operative pain and acute pain as renal colic pains are excluded from the scope of the re-assessment.

The proprietary medicinal products concerned by the re-assessment are ACTISKENAN, MORPHINE AGUETTANT, MORPHINE COOPER, MORPHINE LAVOISIER, MORPHINE RENAUDIN, MOSCONTIN, MOSCONTIN LP, ORAMORPH, NALBUPHINE AGUETTANT, NALBUPHINE MYLAN, NALBUPHINE RENAUDIN, NALBUPHINE SERB, PETHIDINE RENAUDIN, SEVREDOL, SKENAN LP and TEMGESIC.

03 ADMINISTRATIVE AND REGULATORY INFORMATION

The proprietary medicinal products concerned by the re-assessment are listed in Table 1.

These proprietary medicinal products must all be prescribed using a secure prescription form complying with the requirements established in the decree of 31 March 1999.

Morphine-based and pethidine-based proprietary medicinal products are part of the narcotics list with prescription limited to:

- 28 days for oral morphine-based proprietary medicinal products;
- 7 days, or 28 days when administered via an active infusion system, for injectable morphine-based proprietary medicinal products;
- 7 days for pethidine-based proprietary medicinal products.

Buprenorphine- and nalbuphine-based proprietary medicinal products are part of List I.

Table 1: Proprietary medicinal products concerned by the re-assessment

Proprietary Medicinal Product Company	MA Indications	List	Date of MA (Procedure)
Prolonged-release oral MORPHINE-based proprietary medicinal products¹			
MOSCONTIN Prolonged-release coated tablet: 10, 30, 60, 100, 200 mg <i>MUNDIPHARMA</i>	Persistent severe pain or resistant to weaker analgesics, particularly cancer pain.	National Health Insurance (65%) Hospital use B/60 and B/70: Hospital use	10 mg, 30 mg, 60 mg, 100 mg: 2 May 1986 LP 200 mg: 18 January 1994 (national)
SKENAN LP Prolonged-release microgranules in hard capsule: 10, 30, 60, 100, 200 mg <i>BRISTOL-MYERS SQUIBB</i>	Persistent severe pain resistant to other analgesics, particularly cancer pain.	National Health Insurance (65%) + Hospital use LP 200 mg B/28: Hospital use	10 mg, 30 mg, 60 mg, 100 mg: 28 August 1990 200 mg: 11 March 1996 (national)
Immediate-release oral MORPHINE-based proprietary medicinal products¹			
ACTISKENAN Hard capsules: 5, 10, 20, 30 mg <i>BRISTOL-MYERS SQUIBB</i>	Severe pain or intractable pain resistant to weaker analgesics, particularly cancer pain.	National Health Insurance (65%) Hospital use	17 February 1999 (national)
ORAMORPH Oral solution in single-dose container: 10 mg/5 ml, 30 mg/5 ml, 100 mg/5 ml Oral solution in bottle: 20 mg/1 ml <i>NORGINE PHARMA</i>	Severe pain or intractable pain resistant to weaker analgesics, particularly cancer pain.	National Health Insurance (65%) Hospital use	20 mg/ml: 12 January 1994 Other presentations: 28 August 1997 (national)
SEVREDOL Scored film-coated tablet: 10, 20 mg <i>MUNDIPHARMA</i>	Severe pain or intractable pain resistant to weaker analgesics, particularly cancer pain.	National Health Insurance (65%) Hospital use	31 March 1992 (national)
MORPHINE-based proprietary medicinal products for injection¹			
MORPHINE (CHLORHYDRATE) AGUETTANT Solution for injection in ampoule: 0.1 mg/ml, 1 mg/ml, 10 mg/ml, 20 mg/ml, 40 mg/ml <i>AGUETTANT</i>	40 mg/ml dosage: Severe pain and/or intractable pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device. Other dosages: Severe pain and/or intractable pain resistant to weaker analgesics.	National Health Insurance (65%) except 1 mg/ml Hospital use	0.1 mg/ml: 26 December 2003 1 mg/ml: 26 December 2003 10 mg/ml: 26 November 1997 20 mg/ml: 26 November 1997 40 mg/ml: 19 August 1999 (national)
MORPHINE COOPER Solution for injection in ampoule: 10 mg/ml	Severe pain and/or intractable pain resistant to weaker analgesics.	National Health Insurance (65%)	2 September 1994

¹Pure agonist.

Proprietary Medicinal Product Company	MA Indications	List	Date of MA (Procedure)
COOPERATION PHARMACEUTIQUE FRANCAISE			
MORPHINE SANS CONSERVATEUR LAVOISIER (CHLORHYDRATE) Solution for injection in ampoule: 10 mg/1 ml, 20 mg/1 ml MORPHINE (SULFATE) LAVOISIER Solution for injection in ampoule: 1 mg/1 ml, 50 mg/1 ml CHAIX ET DU MARAIS	50 mg/1 ml dosage: Severe pain and/or intractable pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device. Other dosages: Severe pain and/or intractable pain resistant to weaker analgesics.	National Health Insurance (65%) only or Hospital use only Or National Health Insurance + Hospital use	1 mg/ml and 50 mg/1 ml: 28 March 2001 10 mg/1 ml: 10 January 1997 20 mg/1 ml: 8 August 1997 (national)
MORPHINE (CHLORHYDRATE) RENAUDIN Solution for injection in ampoule: 1 mg/ml, 10 mg/ml, 20 mg/ml, 40 mg/ml RENAUDIN	40 mg/ml dosage: Severe pain and/or intractable pain resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device. Other dosages: Severe pain and/or intractable pain resistant to weaker analgesics.	100 ml bag: National Health Insurance (65%) + Hospital use Other presentations: Hospital use	Date of 1 st presentations authorised: 20 January 1998 (national)
BUPRENORPHINE-based proprietary medicinal products²			
TEMGESIC 0.2 mg Sublingual tablet RECKITT BENCKISER HEALTHCARE FRANCE	Severe pain, particularly postoperative pain and tumour pain.	B/20: National Health Insurance (65%) + Hospital use B/50: Hospital use	17 April 1987 (national)
NALBUPHINE-based proprietary medicinal products³			
NALBUPHINE AGUETTANT 20 mg/2 ml Solution for injection in ampoule AGUETTANT	Severe pain and/or intractable pain resistant to weaker analgesics.	Hospital use	16 April 2003 (national)
NALBUPHINE MYLAN 20 mg/2 ml Solution for injection in ampoule MYLAN SAS	Severe pain and/or intractable pain resistant to weaker analgesics.	Hospital use	20 January 1998 (national)
NALBUPHINE RENAUDIN 20 mg/2 ml Solution for injection in ampoule RENAUDIN	Severe pain and/or intractable pain resistant to weaker analgesics.	Hospital use	14 December 2001 (national)
NALBUPHINE SERB 20 mg/2 ml Solution for injection in ampoule SERB	Severe pain and/or intractable pain resistant to weaker analgesics.	Hospital use	B/10: 7 May 2004 B/5: 14 December 2001 (national)
PETHIDINE-based proprietary medicinal products⁴			
PETHIDINE RENAUDIN 50 mg/ml Solution for injection in ampoule RENAUDIN	Severe pain and/or intractable pain resistant to weaker analgesics.	National Health Insurance (15%) Hospital use	28 August 1997 (national)

²Partial agonist.

³Agonist-antagonist.

⁴Pure agonist.

03.1 Reminder of previous assessments

The proprietary medicinal products concerned by the re-assessment are the strong opioids (WHO analgesic ladder step 3) included on the list of refundable medicines and/or on the list of medicines approved for hospital use and marketed.

The tables below give the conclusions of the most recent Transparency Committee (TC) assessments in terms of actual benefit.

Table 1: Prolonged-release oral morphine-based proprietary medicinal products

Proprietary Medicinal Product <i>Company</i>	Indications	Actual Benefit
MOSCONTIN Tablets: 10, 30, 60 and 100 mg MOSCONTIN LP Tablet: 200 mg <i>MUNDIPHARMA</i>	Persistent severe pain or resistant to weaker analgesics, particularly cancer pain.	Substantial RI 27 April 2011
SKENAN LP Microgranules in hard capsule: 10, 30, 60, 100, 200 mg <i>BRISTOL-MYERS SQUIBB</i>	Persistent severe pain or resistant to other analgesics, particularly cancer pain.	Substantial RI 10 February 2010

RI: renewal of inclusion

Table 2: Immediate-release oral morphine-based proprietary medicinal products

Proprietary Medicinal Product <i>Company</i>	Indications	Actual Benefit
ACTISKENAN Hard capsules: 5, 10, 20, 30 mg <i>BRISTOL-MYERS SQUIBB</i>	Severe pain or resistant to weaker analgesics, particularly cancer pain.	Substantial RI 10 February 2010
ORAMORPH Oral solution: 10 mg/5 ml, 30 mg/5 ml, 100 mg/5 ml (single-dose container), 20 mg/1 ml (dropper container) <i>NORGINE</i>	Severe pain or resistant to weaker analgesics, particularly cancer pain.	Substantial RI 1 December 2010
SEVREDOL Scored tablet: 10, 20 mg <i>MUNDIPHARMA</i>	Severe pain or resistant to weaker analgesics, particularly cancer pain.	Substantial RI 27 April 2011

RI: renewal of inclusion.

Table 3: Morphine-based proprietary medicinal products for injection

Proprietary Medicinal Product <i>Company</i>	Indications	Actual Benefit
MORPHINE AGUETTANT Solution for injection in ampoule: 0.1 mg/ml, 1 mg/ml, 10 mg/ml, 20 mg/ml, 40 mg/ml <i>AGUETTANT</i>	0.1 mg/ml, 1 mg/ml, 10 mg/ml, 20 mg/ml Severe pain and/or resistant to weaker analgesics. 40 mg/ml Severe pain and/or resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	Substantial RI 25 May 2011
MORPHINE COOPER Solution for injection in ampoule: 10 mg/ml <i>COOPERATION PHARMACEUTIQUE FRANCAISE</i>	Severe pain and/or resistant to weaker analgesics.	Substantial RI 25 May 2011

Proprietary Medicinal Product Company	Indications	Actual Benefit
MORPHINE (SULFATE) LAVOISIER Solution for injection in ampoule: 1 mg/ml, 50 mg/ml MORPHINE (CHLORHYDRATE) LAVOISIER Solution for injection in ampoule: 10 mg/ml, 20 mg/ml <i>CHAIX ET DU MARAIS</i>	1 mg/ml, 10 mg/ml, 20 mg/ml Severe pain and/or resistant to weaker analgesics. 50 mg/ml Severe pain and/or resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	Substantial RI 3 November 2010
MORPHINE (CHLORHYDRATE) RENAUDIN Solution for injection in ampoule: 1 mg/ml, 10 mg/ml, 20 mg/ml, 40 mg/ml <i>RENAUDIN</i>	1 mg/ml, 10 mg/ml, 20 mg/ml Severe pain and/or resistant to weaker analgesics. 40 mg/ml Severe pain and/or resistant to weaker analgesics requiring treatment with continuous administration of morphine using a programmable medical device.	Substantial Inclusion 30 November 2011 (1 mg/ml, 10 mg/ml, 20 mg/ml) 2 March 2005 (40 mg/ml)

RI: renewal of inclusion.

Table 4: Immediate or prolonged-release proprietary medicinal products containing other strong opioids

Proprietary Medicinal Product Company	Indications	Actual Benefit
Buprenorphine (oral)		
TEMGESIC 0.2 mg Sublingual tablet <i>RB PHARMACEUTICALS LIMITED</i>	Severe pain, particularly post-operative pain and tumour pain.	Substantial RI 18 October 2006
Nalbuphine (for injection)		
NALBUPHINE AGUETTANT 20 mg/2 ml Solution for injection in ampoule <i>AGUETTANT</i> NALBUPHINE MYLAN 20 mg/2 ml Solution for injection in ampoule <i>MYLAN SAS</i> NALBUPHINE RENAUDIN 20 mg/2 ml Solution for injection in ampoule <i>RENAUDIN</i> NALBUPHINE SERB 20 mg/2 ml Solution for injection in ampoule <i>SERB</i>	Severe pain and/or intractable pain resistant to weaker analgesics.	Substantial Inclusion 2 July 2003 (AGUETTANT) 16 October 2004 (SERB)
Pethidine (for injection)		
PETHIDINE RENAUDIN 50 mg/ml Solution for injection in ampoule <i>RENAUDIN</i>	Severe pain and/or intractable pain resistant to weaker analgesics.	Low Re-assessment of actual benefit 18 January 2012

RI: renewal of inclusion.

04 LITERATURE SEARCH

04.1 Data submitted by the pharmaceutical companies

The licence holders were asked to provide HAS with all the clinical information necessary to re-assess the actual benefit of the strong opioids indicated in chronic non-cancer and non-neuropathic pain for which the Transparency Committee has not delivered a specific opinion.

✓ Oral morphine:

For the ACTISKENAN (immediate release) and SKENAN LP (prolonged release) range, the company submitted:

- A double-blind, randomised, placebo-controlled clinical trial⁵ (Chu, 2012) aiming to evaluate the propensity of prolonged-release morphine sulfate to induce tolerance to analgesics or hyperalgesia in low back pain.
- A literature review⁶ (Argoff et al, 2009) aiming to compare the efficacy of short-acting opioids (according to the authors comprising morphine, hydromorphone, oxymorphone, codeine, fentanyl, hydrocodone and oxycodone as well as codeine, hydrocodone and oxycodone in combination with paracetamol or NSAIDs) versus long-acting opioids (comprising methadone, levorphanol and prolonged-release forms of oxycodone, oxymorphone, fentanyl and morphine) in chronic non-cancer pain (CNCP). This review is based on a literature search of clinical trials published between January 1975 and April 2008. The number of articles selected was not indicated by the authors. The opioids' efficacy was evaluated for each pain context (notably osteoarthritis and low back pain). For osteoarthritis, the authors state that the duration of the trials ranged from 2 to 30 weeks and that they can not allow to compare the efficacy of short-acting opioids versus long-acting opioids. For low back pain, there was little data that could be used to evaluate the long-term efficacy of strong opioids.
- American guidelines (ASIPP, 2008) on the use of opioids in non-cancer pain.⁷ These guidelines were updated in 2012.^{8,9}

⁵Chu LF, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blind, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain* 2012; 153: 1583-92.

⁶Argoff et al. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc* 2009; 84: 602-612.

⁷Trescot et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians (ASIPP) Guidelines (2008).

⁸Manchikanti 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.

⁹Manchikanti 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.

For MOSCONTIN (prolonged release) and SEVREDOL (immediate release), the company submitted:

- Two systematic reviews^{10,11} (Papaleontiou, 2010 and Noble, 2008) of the efficacy, safety, abuse and misuse risk data for opioids in the treatment of severe non-cancer pain, particularly in patients aged over 60 years.¹⁰ These data were already examined by the Transparency Committee at the last renewal of inclusion of these proprietary medicinal products. The Committee had considered that the results of these two studies confirmed the favourable efficacy/adverse effects ratio of opioids, including morphine, as a short-term treatment (4 weeks) and that the longer-term results (more than 6 months) were more difficult to interpret. The systematic review by Noble was updated in 2010.¹² The authors included 26 studies with a total of 4893 patients. Twenty-five studies were case studies or non-controlled studies. Depending on the study in question, the opioids examined were considered by the authors as strong opioids (morphine, oxycodone, methadone, oxymorphone and prolonged-release tramadol) or weak opioids (tramadol and dihydrocodeine, but also oxymorphone, buprenorphine and morphine). The opioids were administered orally, transdermally or intrathecally. The authors felt that no solid conclusions could be drawn, due to the limited efficacy and safety data for strong opioids in chronic low back pain and due to methodological weaknesses. This publication is not described in this report.

- A meta-analysis¹³ (Furlan, 2006) aiming to compare the efficacy of opioids to other medicinal products and to placebo in CNCP; identify which types of CNCP respond best to opioids; and determine the most common adverse effects from opioids. This meta-analysis included 41 randomised trials (from 1998 to 2005) corresponding to 6019 patients: 80% of patients had nociceptive pain (osteoarthritis, rheumatoid arthritis or low back pain), 12% had neuropathic pain, 7% had fibromyalgia and 1% had mixed pain. Eight trials were performed versus active comparators. The opioids studied were codeine, tramadol, propoxyphene, morphine and oxycodone, administered orally. The mean duration of treatment was 5 weeks (1 to 16 weeks). For nociceptive pain, the mean duration of treatment was 4.8 weeks (1 to 13 weeks) in 25 studies. This meta-analysis, which was not limited to non-cancer and non-neuropathic pain and which included both strong and weak opioids, is not described in this report.

- A clinical literature review¹⁴ (Avouac, 2007) aiming to determine the analgesic efficacy, the effect on physical functioning and safety of opioids in patients with osteoarthritis.

- An international experts consensus statement¹⁵ (Pergolizzi, 2008), the aims of which included evaluating the benefit of six strong opioids (including buprenorphine and morphine) in the management of chronic non-cancer pain caused by osteoarthritis, rheumatoid arthritis, shingles, etc. in patients aged over 65 years. The authors of this study conclude that, despite the lack of studies performed in elderly patients, opioids are effective in non-cancer pain but need to be adapted to the individual and the safety profile to be taken into account.

¹⁰Papaleontiou A et al. Outcomes associated with opioid use in the treatment of chronic pain in older adults: a systematic review and meta-analysis. *Journal of Drugs and Pharmacology* 2010; 58: 1353-69.

¹¹Noble M. et al. Long term opioid therapy for chronic non-cancer pain: a systematic review and meta-analysis of efficacy and safety. *Journal of Pain and Symptom Management* 2008; 35: 214-228.

¹²Noble M, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Review* 2010, Issue 1. Art. No.: CD006605. DOI: 10.1002/14651858.CD006605.pub2.

¹³Furlan A.D et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006; 174(II): 1589-94.

¹⁴Avouac J et al. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarthritis and Cartilage* 2007; 15: 957-965.

¹⁵Pergolizzi J. et al. Opioids and the management of chronic severe pain in the elderly: Consensus statement of an international expert panel with focus on the 6 clinically most often used World Health Organization step III opioids. *Pain Practice* 2008; 8: 287-313.

- A systematic review¹⁶ (Martell, 2007) of publications from the period 1984-2005 which aimed to determine the prevalence of opioid treatment in chronic low back pain, its efficacy and the prevalence of disorders related to using strong opioids in this indication.

- Three published clinical trials^{5,17,18} (Chu, 2012, Maier, 2002, Caldwell, 2002). The Caldwell trial evaluated the efficacy and safety of oral morphine in moderate to severe chronic osteoarthritis pain for 4 weeks. Due to its short duration and the inclusion of patients with moderate pain, this study is not described in this report. The prospective, placebo-controlled, randomised, double-blind, parallel and crossover Maier study, which was followed by an open-label phase, aimed to evaluate the response rate, efficacy and safety of morphine *versus* placebo in neuropathic (post-herpetic, phantom limb pain, polyneuropathy, myelopathy, etc.) or nociceptive (chronic pancreatitis, spondylolisthesis vertebral lesions, osteoporosis, deformities) chronic non-cancer pain. As the primary endpoint was evaluated after 7 days of treatment, this study is not described in this report concerning chronic pain.

- A follow-up registry¹⁹ (Portenoy, 2007) of patients who took part in efficacy studies of oxycodone in the treatment of pain associated with osteoarthritis, low back pain and diabetic neuropathy. As this was a study of oxycodone, it is not described in this report.

- A clinical trial²⁰ (Tassain, 2003) evaluating the 12-month impact on neuropsychological performance of administering prolonged-release oral morphine in patients who had persistent, moderate to severe non-cancer pain for at least 6 months.

For ORAMORPH (immediate release), the company submitted:

- An open-label clinical trial²¹ (Gatti, 2009) confirming the efficacy and safety of oral forms of morphine in 172 patients aged over 18 years. The results of this study are not presented here as it included both patients with moderate to severe chronic non-cancer pain (58%, n=100) and patients with cancer pain (42%, n=72).

- A clinical trial²² (Gatti, 2010) in 326 patients aged over 18 years. The results of this study are not presented here as it included both patients with moderate to severe chronic non-cancer pain (54%, n=177) and patients with cancer pain (46%, n=149).

- A clinical trial²³ (Lo Presti, 2010), the results of which are not presented here as it was an open-label, non-comparative study including patients with chronic cancer and non-cancer pain.

✓ **Morphine for injection:**

For the MORPHINE LAVOISIER range, the company submitted 24 publications from a literature search. Among these, only the publications by Chu LF et al.⁵ and Katz et al.²⁴ concerned the

¹⁶Martell B A, et al. Systematic review: Opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146: 116-127.

¹⁷Maier 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.

¹⁸Caldwell J R, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J. of Pain and Symptoms Management* 2002; 23: 278-91.

¹⁹Portenoy 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.

²⁰Tassain V, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. *Pain* 2003; 104: 389-400.

²¹Gatti A, et al. Standard therapy with opioids in chronic pain management. *Clin Drug Investig* 2009; 29 Suppl. 1: 17-23.

²²Gatti A, et al. Effects of opioid rotation in chronic pain patients. *Clin Drug Investig* 2010; 30 Suppl.2: 39-47.

²³Lo Presti C, et al. Time to pain relief after immediate-release morphine in episodic pain. The TIME study. *Clin Drug Investig* 2010; 30 Suppl. 2: 49-55.

treatment of chronic pain in rheumatology. The Katz N et al. study (not described in this report) evaluate the efficacy of a combination of morphine sulfate and naltrexone hydrochloride in chronic osteoarthritis pain. The other publications concerned surgical pain or renal colic (indications outside the scope of this re-assessment).

For the MORPHINE RENAUDIN range, the company submitted two studies examining the efficacy of morphine in chronic pain, not detailed here because they are outside the scope of this re-assessment (one study was performed in a surgical context²⁵ and the other aimed to evaluate the association between the placebo effect and psychopathology in patients with chronic low back pain²⁶).

For MORPHINE (CHLORHYDRATE) AGUETTANT and MORPHINE COOPER, the companies did not submit any clinical data relating to chronic non-cancer and non-neuropathic pain.

✓ **Other strong opioids:**

For TEMGESIC (oral buprenorphine), the company submitted three publications:

- A prospective, randomised, double-blind clinical trial²⁷ (James, 2010) comparing sublingual buprenorphine to transdermal buprenorphine as pain management in 246 patients with osteoarthritis. This study is not described in this report as the comparator, transdermal buprenorphine, does not have Marketing Authorisation in France.

- A prospective, randomised, double-blind clinical trial²⁸ (Jalili, 2012) comparing sublingual buprenorphine to intravenous morphine in 45 adult patients with acute bone fracture. This study is not described in this report as the indication acute bone fracture-related pain is outside the scope of this re-assessment.

- An open-label clinical trial²⁹ (Malinoff, 2005) evaluating low-dose sublingual buprenorphine and low-dose combined buprenorphine/naloxone in 95 consecutive patients with chronic non-cancer pain who were undergoing detoxification following long-term opiate analgesic therapy. This study is not described in this report as the indication is outside the scope of this re-assessment.

Nalbuphine for injection

For NALBUPHINE AGUETTANT and NALBUPHINE MYLAN, the companies did not submit any clinical data relating to chronic non-cancer and non-neuropathic pains.

For NALBUPHINE RENAUDIN, the company did not submit any new clinical data relating to chronic non-cancer and non-neuropathic pain, except for follow-up information from routine pharmacovigilance.

For NALBUPHINE SERB, the company submitted an efficacy and safety study of long-term use nalbuphine versus morphine in adult patients with moderate to severe chronic pain caused by

²⁴Katz N, et al. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgraduate Medicine* 2010; 122: 112-28.

²⁵Wai EK, et al. Local administration of morphine for analgesia after autogenous anterior or posterior iliac crest bone graft harvest for spinal fusion: a prospective, randomized, double-blind, placebo-controlled study. *Anesth Analg.* 2010 Mar 1; 110(3): 928-33.

²⁶Wasan AD, et al. The association between psychopathology and placebo analgesia in patients with discogenic lumbar pain. *Pain Med.* 2006 May-Jun; 7(3): 217-28.

²⁷James IG, et al. A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (BuTrans seven-day patches) with buprenorphine sublingual tablets (Temgesic) in patients with osteoarthritis pain. *J Pain Symptom Manage.* 2010; 40: 266-78.

²⁸Jalili M, et al. Sublingual buprenorphine in acute pain management: a double-blind randomized clinical trial. *Ann Emerg Med.* 2012; 59: 276-80.

²⁹Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *Am J Ther.* 2005; 12: 379-84.

advanced cancer.³⁰ This study is not described in this report as it is outside the scope of the indications re-assessed.

Pethidine for injection

The company concerned did not submit any new clinical data relating to chronic non-cancer and non-neuropathic pains, with the exception of follow-up information from routine pharmacovigilance.

04.2 HAS literature search strategy and results

Strategy

A literature search was conducted for the period 2003-2013 and the following sources were consulted:

- For international literature: the Medline database (National Library of Medicine, United States) (see Appendix 1)
- The Cochrane Library (Wiley Interscience, United States)
- Banque de Données en Santé Publique [Public Health Database] (BDSP)
- Websites publishing guidelines and technological or economic assessment reports
- Websites of learned societies competent in the field being studied.

The search was limited to publications in English and French.

Technological assessments, guidelines, consensus conferences, meta-analyses, systematic reviews, randomised and non-randomised controlled trials and comparative studies were sought out.

Results

The following publications were identified:

- A Cochrane Review³¹ (Nüesch et al, 2009) assessing oral opioids (codeine, oxycodone, oxymorphone, morphine) and transdermal opioids (fentanyl) in osteoarthritis of the hip and knee.
- A Cochrane Review³² (Chaparro et al, 2013) assessing opioids versus placebo in chronic low back pain.
- A Cochrane Review³³ (Whittle SL et al, 2011) assessing opioids in rheumatoid arthritis pain.
- A systematic literature review³⁴ (Manchikanti L. et al, 2011).
- The guidelines mentioned in section 09.

05 CLINICAL EFFICACY DATA

05.1 Chronic non-cancer pains of various origins

The authors of the American guidelines⁸ (ASIPP, 2012) carried out an exhaustive review of the scientific literature on the use of opioids to manage non-cancer pains and selected five studies to

³⁰Stambaugh JE. Evaluation of nalbuphine: efficacy and safety in the management of chronic pain associated with advanced pain. *Cur Ther Res* 1982; 31: 393-401.

³¹Nüesch 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.

³²Chaparro LE et al. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8, Art. No.: CD004959.DOI: 10.1002/14651858.CD004959.pub4.

³³Whittle 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.

³⁴Manchikanti L. et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011; 14: 91-121.

assess the efficacy of prolonged-release oral morphine versus various comparators (transdermal fentanyl, dihydrocodeine, buprenorphine or placebo):

- The open-label Allan et al. study (2005)³⁵ evaluated the efficacy of prolonged-release morphine versus transdermal fentanyl in 680 strong-opioid-naïve patients with chronic low back pain. The efficacy endpoints were pain reduction, quality of life and progression of the disease. After 56 weeks of follow-up, the patients in the morphine group who were still included in the study showed a significant improvement in pain score (measured using a visual analogue scale (VAS)). Rescue analgesics (fast-acting opioids) were commonly used (in 50% of patients). The adverse event encountered in the morphine group was constipation. At the end of the study, the authors concluded that 45% of patients had stabilised, 8% had worsened and 23% had improved.

- The Caldwell et al. study (2002)¹⁸ evaluated the efficacy of prolonged-release morphine in 181 patients with moderate to severe chronic osteoarthritis pain in the context of an open-label extension phase of a 4-week randomised trial.

- The Zenz et al. study (1992)³⁶ evaluated the long-term efficacy of oral opioids (morphine, dihydrocodeine and buprenorphine) in chronic non-cancer pain (including neuropathic pain) in 100 patients of whom 23 received morphine. The severity of the pain reduced markedly in 51 patients, partially in 28 patients and not at all in 21 patients.

- The Maier et al. study (2005)³⁷ evaluated the long-term (5-year follow-up) efficacy of morphine in 121 patients with chronic non-cancer pain (including neuropathic pain) who were questioned by telephone or during a visit. The mean duration of treatment was 66 months (37-105 months). Patients reported that in comparison with the start of treatment, their pain was significantly less severe, they were more satisfied with their pain management and their physical functioning and overall quality of life had improved. The treatment discontinuation rate was 14.8%, mainly motivated by lack of efficacy. The authors did not detect any particular signs of tolerance to opioids developing.

- The Tassain et al. study (2003)²⁰ evaluated the neuropsychological impact of long-term (1-year follow-up) treatment with prolonged-release morphine in the small number of 18 patients with chronic non-cancer pain. This prospective study included 28 opioid-naïve patients aged between 18 and 65 years who had lumbosciatic pain, osteoarthritis, spinal disease, post-surgical lesions or multiple sclerosis. Patients could take concomitant analgesic and psychotropic treatments. Ten of the 28 patients stopped treatment during the titration phase as a result of substantial adverse effects or insufficient pain relief, three stopped after 3 months of treatment and only 11 patients were followed up for 12 months. Six out of 11 patients had constipation after one year of treatment.

It should be noted that the authors of the American guidelines⁸ did not identify any studies conducted with oral buprenorphine (only transdermal buprenorphine).

A systematic literature review³⁴ (Manchikanti L. et al, 2011) identified randomised controlled trials of strong opioids for non-cancer pain in patients in whom non-opioid treatment had failed, which took place over a period of more than 12 weeks. Only four studies that examined morphine were identified, and only one of these used correct methodology: a study evaluating a combination of morphine sulfate and dextromethorphan hydrobromide.³⁸ The authors conclude that data from methodologically correct studies of strong opioids in chronic non-cancer pain (more than 12 weeks) are poor.

³⁵Allan L, et al. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic lumbar pain. *Spine (Phila Pa 1976)*. 2005; 30: 2484-90.

³⁶Zenz M, et al. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage* 1992; 7: 69-77.

³⁷Maier C, et al. Long-term efficiency of opioid medication in patients with chronic non-cancer-associated pain. Results of a survey 5 years after onset of medical treatment. *Schmerz*. 2005; 19: 410-7.

³⁸Galer BS et al. MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. *Pain* 2005; 115: 284-95. ePub 2005 Apr 20.

05.2 Chronic pains in osteoarthritis

A literature review¹⁴ (Avouac et al, 2007) carried out using electronic databases up to October 2006 aimed to determine the analgesic efficacy, effect on physical functioning and safety of opioids in patients with osteoarthritis.

All randomised controlled trials evaluating the efficacy and/or safety of opioids versus placebo or non-opioid analgesics in patients with osteoarthritis (4856 patients with a mean age of 61.6 years $\pm$ 3 years) were selected (patients who used opioids after a knee or hip operation were excluded). 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, [1.2-72 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 improvement in functioning (WOMAC).

In comparison with placebo, opioids reduced the severity of osteoarthritis pain with a functional benefit judged to be modest (pooled effect of strong opioids on pain severity: -1.08 (95% CI -1.52 to -0.65); there was substantial heterogeneity ($Q=165.8$, $p<0.0001$)).

This literature review can not allow to assess the long-term efficacy of opioids in osteoarthritis as the mean duration of the trials is too short.

A Cochrane Review³¹ evaluated oral opioids (codeine, oxycodone, oxymorphone, morphine) and transdermal opioids (fentanyl) in osteoarthritis of the hip and knee. This review included 10 studies (with 2268 patients) but only one study looked at morphine. 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. The authors did not recommend using them in these diseases, even in cases of severe pain.

05.3 Chronic low back pain

A randomised, controlled, double-blind clinical trial⁵ (Chu et al, 2012) aimed to evaluate the propensity of prolonged-release oral morphine sulfate to induce tolerance to analgesics or hyperalgesia and the efficacy of morphine sulphate in low back pain. Efficacy was evaluated after one month of treatment, in accordance with European Medicines Agency guidelines for evaluating treatments for moderate to severe chronic pain. Patients were then followed up for an additional year during which no particular treatment was required.

Patients could be either naive or non-naive to opioid treatment, were aged 18 to 70 years, had non-cancer, non-radicular low back pain for at least 6 months, and had a pain score of at least 40 on a VAS (corresponding to moderate to severe pain). Patients were randomised to receive either oral morphine sulfate (with the dose determined and adjusted according to their needs) or a placebo. The study included both opioid-naive and non-opioid-naive patients ($n=69$ in the morphine group, $n=70$ in the placebo group).

The primary endpoints of the study were hyperalgesia (measured by pain tolerance and pain threshold) and/or tolerance to analgesics (tested using remifentanyl infusion). After 1 month of treatment at a mean dose of 78.3 mg/day for patients in the morphine sulfate group, no significant hyperalgesia was observed in either treatment group. Pain tolerance (i.e. maximum pain tolerated) was not affected by treatment. Pain threshold (i.e. transition from a sensation of heat or cold to a sensation of pain) differed significantly from baseline in both groups, but no significant difference was demonstrated between the groups. A significant increase in tolerance to analgesics was observed in patients treated with morphine sulfate but not in those receiving placebo.

The Martell et al. systematic review¹⁶ of publications from the period 1984-2005 aimed to determine the prevalence of opioid treatment in chronic low back pain, its efficacy and the prevalence of problems related to using strong opioids in this indication. 35 studies were selected: 11 on the prevalence of opioid prescribing in chronic low back pain, 15 on efficacy and 9 on the

prevalence of misuse and aberrant behaviours in opioid treatment. Morphine was used at a mean dosage of 73 mg/day (between 30 and 232 mg/day). Results were evaluated in the short term after less than 4 months of treatment.

A Cochrane Review³² evaluated the efficacy of opioids in chronic low back pain. This review included 15 studies (5540 patients) with seven studies examining strong opioids (morphine (two studies), hydromorphone, oxycodone, oxymorphone and tapentadol). No studies were identified with a duration greater than 4 months.

These different studies does not allow to evaluate the long-term efficacy (more than 4 months) of opioids in chronic low back pain.

06 CLINICAL SAFETY DATA

06.1 Pharmacovigilance data from PSURs

6.1.1 ACTISKENAN – SKENAN LP

Analysis of the PSURs covering the periods from 1 July 2001 to 13 October 2009 and 14 October 2009 to 13 October 2012 did not reveal any new signals.

6.1.2 MORPHINE (CHLORHYDRATE) RENAUDIN

Analysis of the PSURs covering the period from 1 January 2005 to 1 September 2012 did not reveal any new signals.

6.1.3 MOSCONTIN – SEVREDOL

Analysis of international data covering the period from 27 May 2006 to 31 October 2009 in the context of the European PSUR synchronisation initiative and of national data covering the period from 27 May 2004 to 31 October 2009 did not reveal any new signals.

An application to change the “Undesirable effects” section of the SmPCs for morphine-based proprietary medicinal products, as for oxycodone and hydromorphone, is under assessment by the ANSM [National Medicines and Health Products Safety Agency] since 2009.

6.1.4 NALBUPHINE RENAUDIN 20 mg/2 ml

Analysis of the PSURs covering the periods from 14 December 2001 to 15 December 2006 and 14 December 2006 to 13 December 2009 did not reveal any new signals.

6.1.5 NALBUPHINE SERB 20 mg/2 ml

Analysis of the PSURs covering the periods from 1 January 2003 to 30 June 2003, 1 July 2003 to 31 December 2003, 1 January 2004 to 30 June 2006 and 1 July 2006 to 14 April 2011 did not reveal any new signals.

6.1.6 ORAMORPH

Analysis of the PSUR covering the period 1 November 2009 to 31 October 2012 did not reveal any new signals.

6.1.7 PETHIDINE RENAUDIN 50 mg/ml

Analysis of the PSURs covering the periods from 28 August 1997 to 28 August 2007 and 29 August 2007 to 28 August 2010 did not reveal any new signals.

6.1.8 TEMGESIC

Analysis of the PSUR covering the period 31 July 2009 to 31 July 2011 did not reveal any new signals.

06.2 Data from the literature

No clinical trial data were identified that could be used to assess the long-term safety, i.e. over more than 4 months, of opioids in chronic non-cancer and non-neuropathic pain.

The most common adverse events for strong opioids in chronic pain are:³⁹

- Constipation, observed in 84% of cases in some series, depending on the preventive measures taken at the time of the initial morphine prescription. Constipation does not resolve during treatment. Systematic prevention combining 1 or even 2 laxatives with appropriate dietary and lifestyle measures (physical activity where possible, adequate fluid intake, balanced diet) is essential.
- Nausea and vomiting, ranging from 20% to 60% depending on the series and the doses used. These side effects are present at the start of treatment and generally improve within 2 to 3 weeks.
- Vertigo, drowsiness, skin dryness and pruritus are fairly common side effects which usually regress after a few days of treatment. Nonetheless, it is common for cognitive slowing to persist and this should be kept in mind, with car or vehicle drivers warned.
- Urinary retention and dysuria are more common in elderly patients and patients with a prostate adenoma.
- Mind-altering effects may occur, particularly in elderly patients.
- Respiratory depression is exceptional when the dosage is adapted to the severity of the pain and increased gradually. It only seems to occur in cases of overdose or associated drug addiction.

Drug tolerance (or dependence) is defined as a reduction in the pharmacological effect or the need to increase doses in order to maintain this effect.³⁹ Tolerance to opioids seems to depend on the nature of the drug, the route of administration and the dosage schedule.

In animals, the presence of a noxious stimulus seems to be the main factor for revert the development of tolerance to opioids. In humans, Tolerance to opioids seems to remain a priori very rare. On the other hand, most side effects induced by morphine, with the exception of constipation, are subject to tolerance.

Dependence can be physical or psychological.³⁹ Physical dependence is a pharmacological phenomenon and its symptoms (withdrawal syndrome) can be prevented by disallowing concomitant administration of an antagonist and progressively decreasing doses when the dosage is to be reduced or the treatment stopped. Psychological dependence or addiction is related to a pathological behaviour characterised by an irrepressible desire to use the product and a progressive lack of interest in other activities or obligations in favour of using it. Psychological dependence on opioids ranges from 0% to 24% depending on the series, but a good number of authors report that if patients are selected and there is regular medical follow-up, the frequency of cases of abuse or psychological dependence does not seem to exceed 1%. Nonetheless, no patient is exempt from the risk of addiction and patients should be routinely monitored at each consultation for the signs: repeatedly losing prescriptions, seeking the medicine from multiple

³⁹Bertin P, et al. Opioïdes forts et douleurs chroniques non cancéreuses rhumatologiques. Médecine. January 2008.

doctors, deteriorating social or family relationships, overconsumption of alcohol or an illicit substance, rapidly increasing doses or not complying with the dosage prescribed, hostility towards changes in treatment despite troublesome adverse effects, etc.

07 OTHER DATA

07.1 Prescription data

The prescription and usage data from the IMS panel as a moving annual total for August 2013 are given in the table below.

Proprietary medicinal product	Number of prescriptions (1000s)	Mean duration of prescriptions (days)	Reason for prescription in rheumatology (number of prescriptions (1000s))
SKENAN LP (prolonged-release microgranules in hard capsule: 10, 30, 60, 100, 200 mg)	389	24.1	Low back pain: 34 Lumbago with sciatica: 27 Compression fracture: 14 Back pain: 9 Osteoarthritis: 8 Joint pain: 4 Arthritis: 2 Polyarthritis: 2 Rheumatoid arthritis: 2 Polyosteoarthritis: 2 Inflammatory spondyloarthritis: 2 Other spondyloarthritis and radicular pain: 1 Osteoarthritis of the knee: 1 Radiculopathy: 1 Ankylosing spondylitis: 1 Spondylarthrosis: 1 Rheumatism: 1
ACTISKENAN (Hard capsule: 5, 10, 20, 30 mg)	211	23.6	Lumbago with sciatica: 17 Low back pain: 11 Osteoarthritis: 8 Back pain: 5 Compression fracture: 5 Other spondylarthrosis: 3 Neck pain: 3 Ankylosing spondylitis: 3 Arthritis: 2 Inflammatory spondyloarthritis: 2 Rheumatoid arthritis: 2 Other osteoarthritis: 1 Osteoarthritis of the knee: 1 Radiculopathy: 1 Scoliosis: 1
TEMGESIC 0.2 mg (sublingual tablet)	21	24.6	Femoral nerve lesion: 3 Other chronic pain: 1 Osteoarthritis: 1
ORAMORPH (oral solution in single-dose container: 10 mg/5 ml, 30 mg/5 ml, 100 mg/5 ml, oral solution: 20 mg/ml)	18	25.6	Back pain: 2
MOSCONTIN (prolonged-release coated tablet: 10, 30, 60, 100, 200 mg)	15	21.5	
SEVREDOL (scored film-coated tablet: 10, 20 mg)	4	19.0	Ankylosing spondylitis: 1
MORPHINE Sans conservateur Lavoisier (Chlorhydrate) 10 mg/1 ml, 20 mg/1 ml, 50 mg/5 ml, 100 mg/5 ml, solution for injection MORPHINE (Sulfate) Lavoisier 1 mg/1 ml, 50 mg/1 ml, solution for injection	3	17.6	

08 SUMMARY & DISCUSSION

The efficacy and safety data available on the use of strong opioids in chronic non-cancer and non-neuropathic pain come primarily from literature reviews. In most cases, these studies include both strong and weak opioids and were conducted for durations of less than 4 months. Therefore, no efficacy and safety data of good methodological quality were identified on the long-term use (more than 4 months' treatment) of strong opioids in chronic non-cancer and non-neuropathic pain.

The information available also cannot be used to assess the phenomena of dependence and drug tolerance.

09 THERAPEUTIC USE

A comprehensive assessment of the pain experienced is an essential prerequisite for pain management.⁴⁰

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 a VAS, pain is said to be moderate when it is rated greater than 4 and severe when it is rated greater 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 severity 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 may be divided into three groups:⁴¹

- **Step 1 analgesics** or non-opioid analgesics currently available are paracetamol, aspirin 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 severe pain. These are the weak opioids, mostly marketed in combination with a non-opioid analgesic, most often paracetamol: codeine combined with paracetamol and/or aspirin or ibuprofen, tramadol alone or combined with paracetamol, opium powder combined with paracetamol, and dihydrocodeine.

- **Step 3 analgesics** are indicated in severe pain and/or resistant to weaker analgesics. These are the pure agonist (morphine, pethidine, fentanyl, hydromorphone, oxycodone), partial agonist (buprenorphine) or agonist-antagonist (nalbuphine) strong opioids.

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

Strong opioids may be used:

- as a short-term treatment for most severe acute pains (post-operative pain, myocardial infarction, renal colic, radicular pain, painful acute exacerbations of a chronic condition, etc.);
- as a long-term treatment for intractable chronic nociceptive pains resistant to step 1 and 2 analgesics. This includes cancer pain where the severity of the pain requires it and not

⁴⁰AFSSAPS [French Healthcare Products Safety Agency]. SFR [French Society of Rheumatology]. SFETD [French Society of Study and Treatment of Pain]. Prise en charge des douleurs de l'adulte modérées à intenses. Mise au point. May 2011 update.

just as part of end-of-life care, and some non-cancer pains that are resistant to all other forms of treatment (neuropathic pain, etc.).

This re-assessment covers chronic non-cancer and non-neuropathic pain, notably including rheumatic pain occurring in the context of low back pain and osteoarthritis.

In chronic non-cancer pain:

Chronic non-cancer pains are a complex and multifactorial syndrome that is considerably influenced by psychological, social and environmental factors. It requires a multi-pronged approach, including treatment of the causative disease, pharmacological and non-pharmacological analgesic treatment and psychosocial and occupational management.³⁹

In 2004, AFSSAPS⁴¹ stated that “the risk/benefit ratio of strong opioids in chronic non-cancer pain (CNCP) should be carefully assessed in order to avoid using a medicine that could be ineffective or insufficiently effective, cause harmful adverse effects, or even trigger a state of physical and/or psychological dependence in the patient.” “Clinicians should ensure that the physical cause is clearly identified, that the pain is severe and not sufficiently eased by aetiological treatment, and that analgesics other than strong opioids are ineffective when they have been 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 CNCP 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. CNCP requires **comprehensive management**: the patient’s complaint should be assessed taking physical, psychological, social and occupational factors into account.
2. The strategy recommended by WHO pain ladder for using analgesics stepwise in cancer pain treatment does not apply to all chronic pain syndromes.
3. Using strong opioids in CNCP 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 department.
6. The **risks of using** strong opioids must be taken into account:
 - Adverse effects occurrence: 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.
 - The possibility of inducing physical and/or psychological dependence or drug tolerance.
 - Potential endocrine disorders, impaired immune response, or possibly genetic damage resulting from potential genotoxic properties may occur during long-term use.

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 to be minor by the patient and the doctor, without any associated effects such as abuse or dependence.”

⁴¹AFSSAPS. Mise au point sur le bon usage des opioïdes forts dans le traitement des douleurs chroniques non cancéreuses. 2004.

“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 pains occurring on a daily basis, a prolonged-release form is recommended.

- Severe but intermittent pain may justify use of an immediate-release 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 limited published studies confirming their efficacy, their adverse effects, and concerns regarding drug tolerance and dependence.⁴²

In 1999, the Limoges guidelines⁴² 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 rheumatic non-cancer pain. This preliminary work was **updated in 2010**.⁴³ 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 is insufficient clinical data to recommend using one strong opioid over another. Nonetheless, the oral and prolonged-release forms are preferred in the first line.

According to the Limoges guidelines, in osteoarthritis of the hip and knee, strong opioids may be offered if the usually recommended treatments fail or are insufficient, or when surgery is contraindicated or the patient is awaiting surgery. It is preferable to use prolonged-release strong opioids, which act on pain and to a lesser degree on functioning.

The 2003 EULAR (European League Against Rheumatism) guidelines⁴⁴ for osteoarthritis of the knee and the 2005 EULAR guidelines⁴⁵ for osteoarthritis of the hip mention the use of opioids (without specifying whether strong or weak) after paracetamol and NSAIDs fail (inefficacy, intolerance) or where they are contraindicated.

The 2009 OARSI (Osteoarthritis Research Society International) guidelines⁴⁶ recommend using strong opioids in severe pains under exceptional circumstances. Non-pharmacological treatments should be pursued and surgery should be considered.

The 2012 ACR (American College of Rheumatology) guidelines⁴⁷ are exact 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 may only be considered in select patients: after conventional drug and non-drug therapies have failed and where psychological and/or social and occupational factors do not override their use.

⁴²Perrot S et al. Utilisation de la morphine dans les douleurs rhumatologiques non cancéreuses: les recommandations de Limoges. Rev Rhum 1999; 66: 651-657.

⁴³Vergne-Salle P et al. Les opioïdes forts dans les douleurs ostéo-articulaires non cancéreuses : revue de la littérature et recommandations pour la pratique clinique : « les recommandations de Limoges 2010 ». Douleurs Evaluation – Diagnostic – Traitement. 2012; 13: 259-275.

⁴⁴Jordan 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.

⁴⁵Zhang 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.

⁴⁶Henrotin 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.

⁴⁷American College of Rheumatology. Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. 2012.

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 low back pain, strong opioids may only be considered in select patients: after conventional drug and non-drug therapies have failed where psychological and/or social and occupational factors do not override their use, with the aim of improving functioning, to help set up a rehabilitation programme and in patients who are re-assessed very regularly.

In this disease, in **December 2000**, the **ANAES** [National Health Accreditation and Assessment Agency] guidelines⁴⁸ on the diagnosis, management and follow-up of patients with chronic low back pain authorised the use of step 3 opioids under the following limited conditions: *"The use of step 3 analgesics (strong opioids) in chronic low back 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 low back pain**,⁴⁹ 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 low back pain was poor (based on the Maier et al.¹⁷ study) and that they have substantial potential adverse effects, including addiction.

In 2007, the American College of Physicians (ACP) and the American Pain Society published joint guidelines on the diagnosis and management of low back pain.⁵⁰

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 low back 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 pains, tricyclic antidepressants may also be an alternative.

In the UK, in 2009, the NICE guidelines⁵¹ authorised the use of strong opioids for the short-term treatment of severe pains; treatment may be continued after a specialist has re-assessed the efficacy/adverse effects ratio, and tricyclic antidepressants are considered as an alternative.

In Canada, in the absence of data, the guidelines^{52,53} do not recommend using strong opioids such as oxycodone or morphine in low back pain or fibromyalgia.

⁴⁸Agence Nationale d'Accréditation et d'Evaluation en Santé, ANAES. Diagnostic, prise en charge et suivi des malades atteints de lombalgie chronique. December 2000.

⁴⁹Centre fédéral d'expertise des soins de santé. Lombalgie chronique. KCE reports vol. 48B.2006.

⁵⁰Chou 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 2; 147: 478-91.

⁵¹National Institute for Health and Clinical Excellence. Lumbar pain; early management of persistent non-specific lumbar pain. May 2009.

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

The American ASIPP guidelines (2012)⁸ 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)⁸ and American Pain Society (APS, 2009)⁵⁴ 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 pains 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^{52,53} are similar. Opioids should be reserved for patients with defined physical or neuropathic pains that has not responded to non-opioid treatment.

In the UK, the British Pain Society has published good practice guidelines for using opioids in chronic pain.⁵⁵ 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 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 authors⁵⁶ noted the lack of methodologically correct data supporting the use of strong opioids in non-cancer pains 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 guidelines for using opioids in chronic pain⁵⁷ 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, start, 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 pains, which make the following points in particular:

⁵²Kahan 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.

⁵³Kahan 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.

⁵⁴Chou R, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. The Journal of Pain 2009; 10: 113-130.

⁵⁵The British Pain Society. Opioids for persistent pain: good practice. January 2010.

⁵⁶Freynhagen R. et al. Opioids for chronic non-cancer pain. BMJ 2013 29; 346.

⁵⁷Aeschlimann A. et al. Recommandations pour l'usage des opioïdes lors de douleurs chroniques. 1re partie. Schweiz Med Forum 2005; 5: 1203-1209.

- 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 pains, 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;

the Committee considers that in intractable chronic pain caused by mechanical disorders, primarily osteoarthritis and chronic low back 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 may be used 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 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 in osteoarthritis of the hip or knee, in case of severe intractable pain, at a stage where surgery is planned or in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery, 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 recommended pharmacological treatments and physiotherapy have failed. 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 low back pain**, pharmacological and non-pharmacological treatments should be considered in the first instance together with physical measures, particularly physiotherapy- and pharmacology-based approaches: paracetamol as a first-line treatment, then NSAIDs. A weak opioid may also be considered for refractory pain.

Strong opioids may be considered as a last-resort treatment in chronic low back pain, in case of severe intractable pain 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 recommended pharmacological treatments and physiotherapy have failed. Use of an oral form is preferred.

With the exception of severe intractable pain in the mechanical rheumatic diseases osteoarthritis of the knee or hip and chronic low back pain and under the conditions specified above, strong opioids have no role in the therapeutic strategy for chronic non-cancer and non-neuropathic pains, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis. A Cochrane Review⁵⁸ (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.³³

The 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 biotherapies have transformed the prognosis of these diseases.

09.1 Target population

Taking into account their therapeutic use as a last-resort treatment in severe intractable pain in osteoarthritis of the knee or hip and chronic low back pain, after other pharmacological treatments and physiotherapy have failed, a very small proportion of patients with osteoarthritis or low back pain is eligible for strong opioid treatment.

No data were identified that could be used to precisely estimate the population with osteoarthritis or low back pain eligible for treatment with strong opioids.

⁵⁸Whittle 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.

010.1 Actual Benefit

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

► The strong opioid-based medicinal products concerned by this re-assessment are intended as symptomatic treatment.

► The efficacy/adverse effects ratio from these medicinal products is modest.

► The strong opioid-based proprietary medicinal products concerned by this re-assessment may be considered as a last-resort treatment in osteoarthritis of the hip or knee, in case of severe intractable pain, at a stage where surgery is planned and in patients who are not candidates (due to refusal or contraindication) for prosthetic joint replacement surgery, 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 recommended pharmacological treatments and physiotherapy have failed. Use of an oral form is preferred.

Strong opioids have no role in the therapeutic management of osteoarthritis of the fingers.

Strong opioids may be considered as a last-resort treatment in chronic low back pain, in case of severe intractable pain 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 limited as possible, after the other recommended pharmacological treatments and physiotherapy have failed. Use of an oral form is preferred.

With the exception of severe intractable pains in the mechanical rheumatic diseases osteoarthritis of the knee or hip and chronic low back pain and under the conditions specified above, strong opioid-based proprietary medicinal products have no role in the therapeutic strategy for chronic non-cancer and non-neuropathic pains, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

Taking account of these points, the Committee considers that the actual benefit of the strong opioid-based proprietary medicinal products concerned by this re-assessment is:

- **substantial** in the management of severe and/or intractable pain occurring in the context of osteoarthritis of the knee or hip and chronic low back 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 limited 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, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis.

Appendix 1: HAS literature search strategy

Medline bibliographic database

For each subject, the bibliographic database search strategy was constructed using either terms from the thesaurus (descriptors) or free terms (from the title or abstract). These were combined with terms describing the types of studies.

The table below indicates the search strategy for the Medline database. In this table, duplicate references may be present within the different topics and/or types of studies.

Terms used	Search period	Number of references
Strong opioids and chronic pain – Guidelines and consensus conferences	Oct. 2003 – Oct. 2013	M: 22
Step 1 <i>(Pain OR Back Pain OR Chronic Pain OR Joint Diseases/drug therapy)/de OR ((chronic AND pain) OR arthrosis OR arthritis)/ti</i>		
AND		
Step 2 <i>(Buprenorphine OR Temgesic OR Nalbuphine OR Pethidine OR Meperidine OR Actiskenan OR Morphine OR Moscontin OR Skenan OR Sevredol OR oramorph)/ti,ab OR (Morphine OR Buprenorphine OR Nalbuphine OR Meperidine)/de</i>		
AND		
Step 3 <i>(recommendation* OR guideline* OR statement* OR consensus OR position paper)/ti OR health planning guidelines/de OR (practice guideline OR guideline OR Consensus Development Conference OR Consensus Development Conference, NIH)/pt</i>		
Strong opioids and chronic pains – Meta-analyses and literature reviews	Oct. 2003 – Oct. 2013	M: 51
Step 1		
AND		
Step 2		
AND		
Step 4 <i>(metaanalys* OR meta-analys* OR meta analysis OR systematic review* OR systematic overview* OR systematic literature review* OR systematical review* OR systematical overview* OR systematic literature review* OR systematic literature search)/ti OR meta-analysis/pt OR cochrane database syst rev/so</i>		
Buprenorphine, pethidine, nalbuphine and chronic pains – Randomised and non-randomised controlled trials	Oct. 2003 – Oct. 2013	M: 81
Step 1		
AND		
Step 5		
AND		
Step 6 <i>random*/ti,ab OR (random allocation OR double-blind method OR single-blind method OR cross-over studies)/de OR (randomized controlled trial OR Controlled Clinical Trial OR multicenter study)/pt</i>		
Morphine and chronic pains – Randomised and non-randomised controlled trials	Oct. 2008 – Oct. 2013	M: 122
Step 1		
AND		
Step 7		
AND		
Step 6		

*: truncation; de: descriptor; ti: title; ab: abstract; pt: publicationscriptor; ti: title; ab: abstract; pt: publication type; so: journal title; M: Medline.