Moderate to severe acute post-operative pain: sufentanil sublingual tablet system

Evidence summary
Published: 30 March 2016
nice.org.uk/guidance/esnm71

Key points from the evidence

The content of this evidence summary was up-to-date in March 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

The sufentanil sublingual tablet system is pre-programmed to dispense a single tablet, on a patient-controlled, as needed basis to manage post-operative pain.

In 2 randomised controlled trials (RCTs), the sufentanil sublingual tablet system was statistically significantly better than placebo at reducing pain intensity over 48 hours following elective major orthopaedic or open abdominal surgery. In a third, open-label RCT with methodological limitations, the sufentanil sublingual tablet system was found to be non-inferior to intravenous (IV) morphine patient-controlled analgesia (PCA) for participant- and nurse-assessed pain control. The European public assessment report (EPAR) states that the risks associated with sufentanil are consistent with other opioids, including the adverse event profile and the abuse potential.

The sufentanil sublingual tablet system may provide an alternative option to IV morphine PCA for some people with moderate to severe acute post-operative pain. Suitable groups may include those who are in relatively good health and for whom improved mobility is an advantage, who can safely use the device and are unlikely to need PCA for more than 72 hours.
**Regulatory status:** The sufentanil sublingual tablet system (Zalviso) received a European marketing authorisation in September 2015. It is anticipated that this product will be launched in September 2016. Sufentanil is classified as a schedule 2 controlled drug subject to the requirements of the Misuse of Drugs Regulations 2001.

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 48 hours, the sufentanil sublingual tablet system:</td>
<td>The sufentanil summary of product characteristics reports that the most common adverse events include nausea and vomiting, and fever. The most serious adverse reaction of sufentanil is respiratory depression. Adverse events were comparable to morphine in the open-label study.</td>
</tr>
<tr>
<td>• was statistically significantly better than placebo at reducing post-operative pain intensity (2 double-blind RCTs, n=426 and n=178).</td>
<td>• The summary of product characteristics provides further information on contraindications, adverse effects and interactions. These are consistent with other opioids.</td>
</tr>
<tr>
<td>• was non-inferior to IV morphine PCA for the primary outcome of participant and nurse reported successful post-operative pain control assessment (1 open-label RCT, n=359).</td>
<td>• According to the EPAR, there is a potential for misdosing with the sufentanil device due to tablet misplacement, and for diversion of dispensed tablets.</td>
</tr>
<tr>
<td>• produced a clinically important 50% pain reduction in over a third of participants in the sufentanil groups, compared with less than a fifth of participants in the placebo groups and was comparable to morphine (EPAR).</td>
<td></td>
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**Patient factors**

- In studies, 6.9% of subjects in the sufentanil group, 11.1% in the IV morphine PCA group and 6.0% in the placebo group experienced adverse events leading to discontinuation (EPAR).
- The sufentanil sublingual tablet system offers another choice for post-operative pain relief with studies finding it to be 'user friendly'.
- Patients should not eat or drink and should minimise talking for 10 minutes after each dose of sufentanil.
- Healthcare professionals should consider the potential for abuse when prescribing or administering sufentanil, and ensure the individual understands how to operate the administration device correctly.
- The sufentanil sublingual tablet system is restricted to use for acute moderate to severe post-operative pain, in the hospital setting and for a maximum duration of 72 hours.

**Resource implications**

- The cost of sufentanil sublingual tablet system is confidential until launch. It is likely that the cost of sufentanil tablets and the administration device will be significantly more than the current standard of care, for example IV morphine PCA.
- IV morphine PCA costs £5.25 for a 50 ml vial of morphine sulfate 1 mg/1ml for intravenous infusion (British National Formulary [BNF], February 2016). This is the cost of morphine sulfate only (excluding VAT) and does not include any procurement discounts or the cost of administration.

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**Introduction and current guidance**

Acute pain is the body’s normal response to tissue damage, following injury or trauma, such as surgery. Of people who have surgery, almost 60% will experience severe pain in the post-operative period and effective control of this pain can contribute to their recovery and rehabilitation, and prevent progression from acute to chronic pain.
NICE has not published guidance on managing acute post-operative pain. In its core standards, the Faculty of Pain Medicine recommends that, if no national guidance is available, specialist pain management services should consider the development, approval and implementation of local pain management protocols and prescribing guidance. All patients with acute pain should have an individualised analgesic plan appropriate to their clinical condition that is effective, safe and flexible.

Acute pain following injury or trauma, responds well to analgesic medicines such as paracetamol, nonsteroidal anti-inflammatory drugs and opioids, with the desired outcome being mild or no pain with minimal adverse effects. In its advice on opioids for managing acute pain, the Faculty of Pain Medicine advises that opioids may be less effective for acute pain than medicines with other mechanisms of action, and that they are best used in combination with other analgesics and local anaesthetics as appropriate. See the Core standards for pain management services in the UK for more information.

People who undergo surgery may control post-operative pain by self-administering small doses of IV opioid (such as morphine) using programmable pumps (patient-controlled analgesia or PCA). There is moderate to low quality evidence that PCA is an effective alternative for post-operative analgesia, with slightly better pain control and increased patient satisfaction when compared with non-patient controlled methods (McNichol et al. 2015). See the Full text of introduction and current guidance.

**Product overview**

Sufentanil (Zalviso) is indicated for the management of moderate to severe acute post-operative pain in adults, in a hospital setting only. It should be prescribed only by physicians who are experienced in the management of opioid therapy, particularly opioid adverse events such as respiratory depression. Sufentanil is self-administered sublingually leading to rapid analgesia. Sufentanil is classified as a schedule 2 controlled drug subject to the requirements of the Misuse of Drugs Regulations 2001. Prescribing guidance for controlled drugs can be found in the BNF and the NICE guidance on the safe use and management of controlled drugs.

The administration device, which contains a cartridge of 40 sufentanil 15 micrograms sublingual tablets, is pre-programmed to dispense a single tablet on a patient-controlled, as needed basis, with a minimum of 20 minutes (lockout interval) between doses, over a period of up to 72 hours (the maximum recommended treatment duration, summary of product characteristics).
According to the marketing authorisation holder, the sufentanil sublingual tablet system has a number of built-in security features to minimise unauthorised access to, and dispensing of the tablets. These include a locked in tamper-resistant tablet cartridge, visible and audible alarms indicating if the dispenser has been pried from the controller, a tethering cable to secure the device to the bedrail, an adhesive patient thumb tag paired with the device to reduce the risk of ‘proxy’ dosing, and an authorised access card for each healthcare professional interacting with the system. The device programming cannot be overridden to increase the frequency of dispensing (personal communication, Grünenthal Ltd).

Full text of product overview.

Evidence review

- In 2 RCTs, conducted in US hospitals, the sufentanil sublingual tablet system was statistically significantly better at reducing pain intensity over 48 hours following elective major surgery compared with placebo. Treatment differences for time-weighted summed pain intensity difference (SPID) were 87.6 (95% CI 66.2 to 109.0, p<0.001) following knee and hip replacement (Jove et al. 2015) and 50.0 (95% CI 19.9 to 80.1, p=0.001) after open abdominal surgery (Ringold et al. 2015). However, these outcomes are difficult to interpret and the clinical importance of these findings is unclear.

- In the 2 RCTs (Jove et al. 2015 and Ringold et al. 2015), participant withdrawals due to inadequate analgesia were statistically significantly less frequent in the sufentanil group compared with placebo (14.3% compared with 48.1% of people following hip or knee replacement, p<0.001 and 17.4% compared with 31.6% after open abdominal surgery, p=0.035, for sufentanil and placebo respectively).

- Participants and nurses each rated the overall ease-of-care of the system as greater than 4 on the 0 to 5-point scale (where 0 is not at all and 5 is a very great deal) in both RCTs, suggesting that the device was easy to use.

- In Melson et al. 2014, a phase III randomised, open-label, non-inferiority trial, sufentanil was compared with the current standard of care, IV morphine PCA, for the management of acute post-operative pain following major open abdominal or hip or knee replacement surgery. The treatment difference for the proportion of participants reporting successful pain control achieved the predefined criteria for non-inferiority of sufentanil compared with morphine, and superiority over morphine was also demonstrated (treatment difference 12.9%, p=0.007). However, the clinical importance of the difference between the 2 treatments for these outcomes is difficult to interpret and according to the EPAR the strength of the primary
end-point is uncertain. As this trial was performed in addition to the 2 RCTs the Committee for Medicinal Products for Human Use (CHMP) agreed that it could be accepted as supportive evidence for efficacy of the sufentanil sublingual tablet system.

- For secondary endpoints, there was no significant difference between sufentanil and morphine for pain intensity (p=0.569) or pain relief (p=0.055) over 48 hours. Participant withdrawals due to inadequate analgesia were less frequent in the sufentanil group compared with the morphine group (7.3% compared with 8.9%, no analysis reported).

- Participants and nurses were statistically significantly satisfied with the sufentanil sublingual tablet system (p=0.004 and p<0.001 respectively) and rated it as easy to use (p<0.001 and p=0.017 respectively), compared with IV PCA morphine. However these results may be subject to bias because participants and nurses were aware of which treatment had been allocated due to the open-label study design.

- The EPAR reports that, because the primary endpoint was difficult to interpret, the CHMP requested further responder analyses to be performed to determine the clinical relevance of the achieved effect in pain reduction with sufentanil sublingual tablet system from the results of the 3 studies. These post-hoc analyses for Ringold et al. 2015 and Jove et al. 2015 showed that a clinically important 50% pain reduction was achieved in 37% and 31% of sufentanil participants in these trials compared with 17.5% and 9.6% of placebo participants. The responder analysis for Melson et al. 2014, comparing sufentanil and morphine, determined there was a similar clinically important pain reduction in both treatment groups (30% and 32% of participants, respectively). The CHMP concluded that the 3 phase III studies provide sufficient evidence of the efficacy of sufentanil sublingual tablets in acute post-operative pain.

- The EPAR states that during phase II and phase III trials, 685 people were exposed to the proposed marketed dose of sublingual sufentanil. However, there is wider experience with IV and epidural sufentanil in other countries outside of the UK. According to the EPAR, the risks associated with sublingual sufentanil are in line with the well-known class effects of opioids, including the adverse event profile and abuse potential.

- In the phase III, placebo-controlled trials (Jove et al. 2015 and Ringold et al. 2015) the most common adverse events included nausea (46.9% in the sufentanil group and 36.4% in the placebo group), pyrexia (17.7% compared with 11.1%) and vomiting (11.7% compared with 6.2%). In the open-label phase III trial (Melson et al. 2014), which compared sufentanil with morphine, the rates of common opioid adverse events were similar. The summary of product characteristics provides further information on contraindications, adverse effects and interactions of sufentanil.
The CHMP concluded that safety and efficacy data from the 3 key studies of sufentanil sublingual could not be extrapolated to other acute pain indications, longer duration of treatment or other clinical settings; therefore, the marketing authorisation for the sufentanil sublingual tablet system is restricted to moderate to severe acute post-operative pain in a hospital setting for up to 72 hours (European public assessment report).

The studies only included people in relative good health who were undergoing elective major open abdominal and hip and knee replacement, limiting generalisability to other populations or types of surgery. People on chronic opioid therapy were excluded from all 3 phase III RCTs, and people with a history of alcohol or opioid abuse were excluded from the 2 placebo controlled studies (Jove et al. 2015 and Ringold et al. 2015). Data on using sufentanil sublingually for post-operative pain in these populations are limited. The summary of product characteristics reports that people on chronic opioid therapy or opioid addicts may require higher analgesic doses than the sufentanil sublingual tablet administration device can deliver.

In 2014, the US Federal Drug Administration (FDA) did not approve a new drug application for the sufentanil sublingual tablet system and to ensure proper use of the device, has requested additional information from the manufacturer before it can reconsider a marketing application. A trial evaluating the usability and functionality of the sufentanil sublingual tablet system is due to start in 2016 (Clinical trials identifier NCT02662764).

Full text of evidence review.

Context

Acute pain responds well to analgesic medicines such as paracetamol, nonsteroidal anti-inflammatory drugs and opioids. According to the British National Formulary (BNF) a combination of opioid and non-opioid analgesics is used to treat post-operative pain and that consulting hospital protocols for details of PCA is advisable.

The cost of the sufentanil sublingual tablet system is confidential until launch. The current opioid of choice for PCA is IV morphine (European public assessment report), which costs £5.25 for a 50 ml vial of morphine sulfate 1 mg/1ml for intravenous infusion (BNF, February 2016). This is the cost of morphine sulfate only (excluding VAT) and does not include any procurement discounts or other costs incurred, such as administration. Other examples of opioids that are used for post-operative analgesia include fentanyl (PCA), oxycodone (PCA or orally) and diamorphine (PCA). The cost of other opioid analgesics will depend on the preparation chosen and the dosage used, in addition to any procurement discount and other associated costs.
Estimated impact for the NHS

A potential benefit of the sufentanil sublingual tablet system is as an alternative to IV PCA, therefore avoiding some associated problems and with improved mobility of the patient. However, specialists consulted during the development of this evidence summary advised that any individual having major surgery sufficient to need strong opioid analgesia will likely have an IV infusion in situ. Specialists advised that moving away from IV infusions encourages mobility and compliance with physiotherapy goals and subsequently the use of oral opioids in these situations is considered to be increasing. The disadvantage of oral opioids is the nursing time required to administer controlled drugs to the patient and using a PCA system mitigates for this. The risks of moving around whilst taking strong opioids are the same, irrespective of the mode of analgesia.

In studies with identified methodological weaknesses, the sufentanil sublingual tablet system has been shown to be a user friendly device, which is better than placebo and comparable to IV morphine PCA at reducing post-operative pain, with an adverse event and abuse risk consistent with other opioids. There is a potential for misdosing with the device due to tablet misplacement and a potential risk of diversion once the tablet has been dispensed. The summary of product characteristics warns that the potential for abuse should be considered when prescribing or administering sufentanil where there is concern about an increased risk of misuse, abuse or diversion.

Educational materials are available for healthcare professionals, which provide guidance on appropriate use of the system and minimising risk.

The summary of product characteristics states that before the sufentanil sublingual tablet system is used, healthcare professionals should ensure that patients understand how to operate the administration device correctly. Only patients who are able to understand and follow the instructions to operate the administration device should use sufentanil sublingual tablets and the ability of the patient to use the device appropriately should be taken into consideration by prescribers. For example, the person’s visual or cognitive function and manual dexterity will need to be taken into account. Prescribers should also note that the marketing authorisation for sufentanil sublingual tablet system is restricted to 72 hours duration for the management of post-operative pain. Consequently it may be necessary to alter analgesia for patients requiring treatment for longer than this.
As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of the sufentanil. The cost of the sufentanil sublingual tablet system is not yet known. It is likely that the cost of sufentanil tablets and the administration device will be significantly more than the current standard of care, for example the cost of IV morphine PCA. Maintenance costs for the administration device will be covered during the 2 year warranty period (personal communication Grünenthal Ltd).

Full text of estimated impact for the NHS.

About this evidence summary

Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Acute pain is defined as pain of recent onset, of limited duration and usually related to a pathological process, disease or injury. Of people who undergo surgery, almost 60% experience severe pain in the post-operative period. As well as reducing pain, effective acute post-operative pain control contributes to recovery and rehabilitation, and prevents progression from acute to chronic pain (the Faculty of Pain Medicine of the Royal College of Anaesthetists [2015] Core standards for pain management services in the UK).

NICE has not published guidance on managing acute post-operative pain. In its core standards, the Faculty of Pain Medicine recommends that, if no national guidance is available, specialist pain management services should consider the development, approval and implementation of local pain management protocols and prescribing guidance. Acute pain management should be supervised by consultants and specialist nurses with appropriate training and competencies. All patients with acute pain should have an individualised analgesic plan appropriate to their clinical condition that is effective, safe and flexible. Based on the pain assessment, there must be clear protocols for the management of acute pain by ward staff, which are easily accessible, and with support from the specialists when appropriate.
Acute pain following injury or trauma, responds well to analgesic medicines such as paracetamol, nonsteroidal anti-inflammatory drugs and opioids, with the desired outcome being mild or no pain with minimal adverse effects. In its advice on opioids for managing acute pain, the Faculty of Pain Medicine advises that opioids may be less effective for acute pain than medicines with other mechanisms of action, and that they are best used in combination with other analgesics and local anaesthetics as appropriate (a multimodal approach). Adverse effects of analgesic medicines are relatively common and need to be balanced against efficacy. Opioid treatment should not continue beyond the expected period of tissue healing. See the Core standards for pain management services in the UK for more information.

People who undergo surgery may control post-operative pain by self-administering small doses of intravenous (IV) opioid (such as morphine) using programmable pumps (patient-controlled analgesia or PCA). Studies have shown that PCA is often preferred over traditional methods of pain management, such as a nurse administering an analgesic at the patient's request. A Cochrane review (49 randomised controlled trials [RCTs], n=1,725) found moderate to low quality evidence that PCA is an effective alternative to non-patient-controlled systemic analgesia for post-operative pain control. PCA improved patient satisfaction and, although doses of opioid analgesia were slightly higher in people using PCA, as was the occurrence of itching, adverse events were otherwise similar between the groups (McNichol et al. 2015).

**Product overview**

**Drug action**

Sufentanil is a synthetic, potent opioid with highly selective binding to µ-opioid receptors. Analgesia induced by sufentanil has a potency 7 to 10-fold higher than fentanyl and 500 to 1,000-fold higher than morphine (per oral dose). The high lipophilicity of sufentanil allows it to be administered sublingually and achieve a rapid onset of analgesic effect (summary of product characteristics for sufentanil).

**Licensed therapeutic indication**

Sufentanil sublingual tablets (Zalviso) received a European marketing authorisation in September 2015. It is anticipated that they will be launched in September 2016. Sufentanil sublingual tablets are indicated for the management of acute moderate to severe post-operative pain in adults, in a hospital setting only. They should be prescribed only by physicians who are experienced in the management of opioid therapy, particularly opioid adverse events such as respiratory depression (summary of product characteristics for sufentanil sublingual tablet system). Sufentanil is classified as a schedule 2 controlled drug subject to the requirements of the
Prescribing guidance for controlled drugs can be found in the BNF and the NICE guidance on the safe use and management of controlled drugs.

**Course and cost**

Sufentanil sublingual tablets are self-administered in response to pain using the manufacturer's administration device. The administration device is pre-programmed to dispense a single sufentanil 15 micrograms sublingual tablet, on a patient-controlled as needed basis, with a minimum of 20 minutes (lockout interval) between doses, over a period of up to 72 hours (the maximum recommended treatment duration). The programming cannot be overridden to increase the frequency of dispensing. The device has a number of other built-in security features to minimise unauthorised access to, and dispensing of, sufentanil sublingual tablets:

- The tamper-resistant cartridge of tablets is mechanically locked into the controller.
- Audible and visible alarms indicate if the dispenser has been pried from the controller.
- The controller is tethered to the patient’s bedrail or other secure object to prevent theft.
- An adhesive patient thumb tag with radio frequency identification pairs the patient to the device and reduces the risk of 'proxy' dosing.
- An authorised access card is required for a healthcare professional to setup, take down and interact with the system. The card does not allow the healthcare professional to dispense a tablet (personal communication, Grünenthal Ltd).

The dispensed sublingual tablet should be dissolved under the tongue and not be crushed, chewed or swallowed. Patients should not eat or drink and should minimise talking for 10 minutes after each dose of sufentanil. The maximum amount of sublingual sufentanil that can be delivered over an hour via the administration device is 45 micrograms (3 doses). In addition, the device has a number of features to discourage and identify possible diversion:

- The system stores detailed a history including the quantity of doses delivered, the number of doses remaining and any attempted doses during the lockout period.
- Shift changes can be recorded to indicate the cumulative number of doses dispensed during each staff shift.
- Separate electronic tablet counts on both the dispensing device and the cartridge can be reconciled to identify possible diversion (personal communication, Grünenthal Ltd).
Each cartridge of sufentanil sublingual tablets contains 40 sufentanil 15 microgram sublingual tablets. The single use cartridge is inserted and locked into the controller. Spent cartridges can be replaced. The controller is designed to dispense 30,000 tablets (750 cartridges) and will be priced separately to the tablet cartridges, as is the case with alternative PCA systems.

The cost of the sufentanil sublingual tablet system is confidential until launch. Maintenance costs will be covered during the 2 year warranty period (personal communication Grünenthal Ltd).

Evidence review

This evidence summary focuses on the evidence for the safety and efficacy of sufentanil from 2 randomised placebo-controlled phase III trials (Jove et al. 2015 and Ringold et al. 2015) and 1 randomised phase III study with an active control (IV morphine PCA, Melson et al. 2014). The 2 placebo-controlled trials are discussed together because their main difference lies in the type of surgery considered: open abdominal (Ringold et al. 2015) and hip or knee replacement (Jove et al. 2015). Information from the European public assessment report (EPAR) for sufentanil has been used to clarify and supplement data from the 3 published studies included in this evidence summary.

According to the literature, clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Pain is generally measured using standard pain intensity scales immediately before the intervention and pain intensity and pain relief scales over the following 4 to 6 hours for shorter acting drugs and up to 12 or 24 hours for longer acting drugs. At least 50% pain relief is typically regarded as clinically important across various pain conditions (Moore et al. 2015).

Sufentanil sublingual tablet system for the management of post-operative pain following knee or hip arthroplasty (Jove et al. 2015) and open abdominal surgery (Ringold et al. 2015)

- Design: 2 multicentre phase III randomised double-blind, placebo-controlled trials (RCTs) evaluating the efficacy and safety of a sufentanil sublingual tablet system for managing post-operative pain in hospital settings.

- Population: participants were recruited from 34 and 13 hospital sites (n=426, Jove et al. 2015 and n=178, Ringold et al. 2015, respectively) in the United States. Adults with sufficient manual dexterity to operate the sufentanil sublingual tablet system who had been classified as having an American Society of Anaesthesiologists physical status of 1 to 3 were included. In Ringold et al. 2015, participants (mean age 55 years, range 23–92 years) were scheduled to undergo open abdominal surgery (including laparoscopically-assisted) under general or spinal
anaesthesia that did not include intrathecal opioids. In Jove et al. 2015, participants (mean age 66 years, range 26–90 years) were scheduled to undergo an open elective total unilateral knee replacement (48%) or total unilateral hip replacement (52%) under general or spinal anaesthesia that did not include intrathecal opioids. At randomisation all participants were post-surgical patients who had been admitted to the post-anaesthesia care unit, who were expected to remain hospitalised and to have acute pain requiring parenteral opioids for at least 48 hours after surgery (with pain intensity of greater than 4 on an 11-point numerical rating scale just before the first dose of study drug). Screening exclusion criteria included people who had taken an opioid for more than 30 consecutive days at a daily dose of more than 15 mg of morphine (or equivalent) within the past 3 months prior to surgery; people with a history of drug or alcohol misuse; people with current sleep apnoea or requiring oxygen; people with a medical condition that would interfere with post-operative pain assessments; and those with a history of allergy to opioids. People with pre-existing chronic pain conditions and those using drugs that could affect pain levels during the study (such as anti-inflammatory agents, steroids or gabapentinoids) were also excluded. At randomisation, exclusions also included people who were not awake or breathing spontaneously, and those who had a respiratory rate of less than 8 breaths per minute or greater than 24 breaths per minute. After randomisation, but before receiving the study drug, participants were required to have had a pain intensity of less than 5 at some point while in the post-anaesthesia care unit to demonstrate that their pain was manageable. They also had to have been discharged or be ready for discharge from the post-anaesthesia care unit, and their reported pain intensity had to escalate back above 4 on the numerical rating scale just before the first dose of study drug (recorded as baseline pain intensity). The patient population was comparable between the sufentanil and placebo arms in both studies. A substantial proportion of participants were 65 years or older (57% and 26% in Jove et al. 2015 and Ringold et al. 2015 respectively). People with a wide range of body mass indexes (BMI) were included (range 12.6 to 62 kg/m²). More female than male participants were enrolled in both studies (61% in Jove et al. 2015 and 74% in Ringold et al. 2015).

- Intervention and comparator: participants were randomised in a 3:1 ratio in Jove et al. 2015 and a 2:1 ratio in Ringold et al. 2015 to receive an administration system dispensing a sublingual 15 microgram sufentanil tablet with a 20-minute lockout period (to prevent a second dose being administered too soon) or an identical system dispensing a sublingual placebo tablet for 48 hours and up to 72 hours. Allocation was concealed. Pain intensity scores were recorded at baseline and for up to 72 hours after starting the study drug. In order to minimise drop-outs and missing data, inadequate analgesia was treated with 2 mg morphine intravenously. Morphine could only be used when 10 minutes had passed since the study drug was taken and no more than once an hour throughout the study. Participants who required further additional analgesia left the study because of inadequate analgesia and could receive any standard analgesic available at the clinical site. Participants who had oxygen saturation
levels that could not be maintained at 95% or greater with or without the use of supplemental oxygen, a respiratory rate less than 8 breaths per minute or excessive sedation could not have the study drug or morphine until their vital signs improved.

- Outcomes: the primary endpoint was time-weighted summed pain intensity difference (SPID) over 48 hours (which is the summed pain intensity difference between each pain evaluation time point and baseline over 48 hours). Pain intensity was measured using an 11-point numerical rating scale (where 0 is no pain and 10 is the worst possible pain). Secondary endpoints included differences in pain intensity (SPID) and total pain relief (TOTPAR, a 5-point scale where 0 is no relief and 4 is complete relief) over 72 hours, the proportion of participants who discontinued treatment or required rescue medication due to inadequate analgesia, and participant and healthcare provider global assessments of the method of pain control (on a 4-point scale where 1 is poor and 4 is excellent). Validated patient and nurse ease-of-care (EOC) questionnaires were completed to assess participant and nurse satisfaction with the sufentanil sublingual tablet system. The patient ease-of-care questionnaire has 23 questions; 21 of which are scored on a scale of 0 to 5 (where 0 is not at all and 5 is a very great deal) and summarised into 6 subscale scores (confidence with the device, comfort with the device, movement, dosing confidence, pain control, and knowledge and understanding) and a total ease-of-care score. The other 2 questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) are scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into an overall satisfaction score. The nurse ease-of-care questionnaire has 22 questions, 20 of which are scored on a scale of 0 to 5 (where 0 is not at all and 5 is a very great deal) and summarised into 2 subscale scores (time-consuming and bothersome) and a total ease-of-care score. Two other questions (satisfaction with the level of pain control and satisfaction with the device) were scored on a 6-point scale (extremely dissatisfied to extremely satisfied) and combined into a total satisfaction score. Efficacy endpoints were analysed using the modified intention-to-treat (mITT) population, which included all randomised participants who received at least 1 dose of study medication. Safety assessments included adverse events, clinical laboratory evaluations, continuous oxygen saturation, and vital signs. Randomised participants who received at least 1 dose of study drug were included in the safety analysis and summaries. Many of the outcomes of these 2 studies are not discussed in this evidence summary because the use of a placebo comparator limits the studies’ application to practice.

**Table 1 Summary of RCTs evaluating the sufentanil sublingual tablet system following knee or hip arthroplasty (Jove et al. 2015) and open abdominal surgery (Ringold et al. 2015)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sufentanil 15 microgram</th>
<th>Placebo</th>
<th>Analysis</th>
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<table>
<thead>
<tr>
<th></th>
<th>Knee or hip arthroplasty</th>
<th>Open abdominal surgery</th>
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<td></td>
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<td></td>
<td>n=119</td>
<td>n=59</td>
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<tr>
<td><strong>Efficacy</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Knee or hip arthroplasty</td>
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<td></td>
<td>Open abdominal surgery</td>
<td>n=115</td>
<td>n=57</td>
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<tr>
<td><strong>Primary outcome: LS mean SPID score at 48 hours (SEM)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Knee or hip arthroplasty</td>
<td>76.2 (7.0) 95% CI 62.4 to 90.1</td>
<td>-11.4 (10.6) 95% CI -32.1 to 9.4</td>
<td>Treatment difference 87.6 (10.9) 95% CI 66.2 to 109.0 p&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Open abdominal surgery</td>
<td>105.6 (10.1) 95% CI 85.9 to 125.6</td>
<td>55.6 (13.1) 95% CI 29.7 to 81.5</td>
<td>Treatment difference 50.0 (15.3) 95% CI 19.9 to 80.1 p=0.001</td>
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</tr>
<tr>
<td><strong>Selected secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LS mean SPID score at 72 hours (SEM)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee or hip arthroplasty</td>
<td>134.6 (11.4) 95% CI 112.1 to 157.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-2.8 (17.1) 95% CI -36.1 to 30.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Treatment difference 137.4 (17.7) 95% CI 102.6 to 172.3 p&lt;0.001</td>
<td></td>
<td></td>
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</table>
### LS mean TOTPAR score at 48 hours (SEM)\(^b\)

<table>
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<tr>
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<th>Knee or hip arthroplasty</th>
<th>Treatment difference</th>
<th>p-value</th>
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<tr>
<td></td>
<td>LS mean (SEM)</td>
<td>LS mean (SEM)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>171.1 (16.2)</td>
<td>100.8 (20.9)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>95% CI 139.1 to 203.0(^c)</td>
<td>95% CI 59.5 to 142.1(^c)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Treatment difference</td>
<td>70.3 (24.3)</td>
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<tr>
<td></td>
<td></td>
<td>95% CI 22.2 to 118.4</td>
<td>p=0.004</td>
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</tr>
<tr>
<td></td>
<td>Knee or hip arthroplasty</td>
<td>91.3 (3.0)</td>
<td>53.5 (4.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI 85.4 to 97.2(^c)</td>
<td>95% CI 44.6 to 62.3(^c)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Treatment difference</td>
<td>37.8 (4.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI 28.7 to 47.0</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Percentage of participants</td>
<td>Knee or hip arthroplasty</td>
<td>14.3% (45/315)</td>
<td>48.1% (50/104)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>discontinuing treatment due to</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>inadequate analgesia over 48</td>
<td>Open abdominal surgery</td>
<td>17.4% (20/115)</td>
<td>31.6% (18/57)</td>
<td>p=0.035</td>
</tr>
<tr>
<td>hours</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Percentage of participants</td>
<td>Knee or hip arthroplasty</td>
<td>50.8% (160/315)</td>
<td>73.1% (76/104)</td>
<td>p&lt;0.001</td>
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<tr>
<td>requiring rescue morphine due to</td>
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<td></td>
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<tr>
<td>inadequate analgesia over 48</td>
<td>Open abdominal surgery</td>
<td>33.0% (38/115)</td>
<td>66.7% (38/57)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>hours</td>
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### Safety\(^d\)

<table>
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<td>Safety</td>
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</tbody>
</table>

\(^{b}\) Differences are based on the least squares means TOTPAR scores at baseline

\(^{c}\) Calculated as the difference between the LS mean (±SEM)

\(^{d}\) Data from a pre-existing study, as the trial dataset did not contain sufficient data to allow further analysis

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## Patients reporting serious adverse events

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<th>Knee or hip arthroplasty</th>
<th>Patients reporting any related adverse events</th>
<th>Knee or hip arthroplasty</th>
<th>Open abdominal surgery</th>
<th>Number of patient withdrawals from study due to adverse events</th>
<th>Knee or hip arthroplasty</th>
<th>Open abdominal surgery</th>
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<td></td>
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<tr>
<td>Open abdominal</td>
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<td>1.9%</td>
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<td>surgery</td>
<td>(1/114)</td>
<td>(6/315)</td>
<td>(0/58)*</td>
<td></td>
<td>(1/114)</td>
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<td>(0/58)</td>
<td>(0/58)</td>
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<td>Knee or hip</td>
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<td>0%</td>
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<td>54.3%</td>
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<td>p&lt;0.001</td>
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<td>(6/315)</td>
<td>(0/58)</td>
<td></td>
<td>(171/315)</td>
<td></td>
<td>(35/104)</td>
<td>(171/315)</td>
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<td>23.7%</td>
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<td>Not statistically</td>
<td>Open abdominal surgery</td>
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<td>(27/114)</td>
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<td>significant</td>
<td>(27/114)</td>
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<td>Number of patient</td>
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<td>6.7%</td>
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<td>8.6%</td>
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<td>(7/104)</td>
<td></td>
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<td>(7/114)</td>
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<td>study due to</td>
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<td>Open abdominal surgery</td>
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<td></td>
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<td></td>
<td></td>
<td>Knee or hip arthroplasty</td>
<td>34.9%</td>
<td>22.1%</td>
<td>No analysis</td>
<td>Knee or hip arthroplasty</td>
</tr>
<tr>
<td>Nausea</td>
<td>(110/315)</td>
<td>(23/104)</td>
<td></td>
<td></td>
<td>(16/114)</td>
<td></td>
<td>reported</td>
<td>(16/114)</td>
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<tr>
<td>Vomiting</td>
<td>Knee or hip arthroplasty</td>
<td>10.8%</td>
<td>5.8%</td>
<td>Open abdominal surgery</td>
<td>3.5%</td>
<td>3.4%</td>
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<td>Open abdominal surgery</td>
</tr>
<tr>
<td></td>
<td>(34/315)</td>
<td>(6/104)</td>
<td></td>
<td></td>
<td>(4/114)</td>
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<td>reported</td>
<td>(4/114)</td>
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<td>Oxygen saturation</td>
<td>Knee or hip arthroplasty</td>
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<td>2.9%</td>
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<td></td>
<td></td>
<td>reported</td>
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<td>decreased</td>
<td>(22/315)</td>
<td>(3/104)</td>
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</tbody>
</table>
Sufentanil sublingual tablet system compared with IV morphine patient-controlled analgesia for the management of acute post-operative pain (Melson et al. 2014)

- Design: a multicentre phase III randomised open-label, active-controlled trial (RCT) evaluating how satisfactory patients found a sufentanil sublingual tablet system for managing post-operative pain in a hospital setting (Melson et al. 2014).

- Population: 359 adults scheduled within 30 days to undergo elective major open abdominal (including laparoscopically-assisted, 22%) or orthopaedic (total hip [45%] or knee [33%] replacement) surgery were recruited from 26 hospitals in the United States. At some point in the recovery room, all participants had reported having acute pain of less than 5 on the 11-point numerical rating scale (where 0 is no pain and 10 is worst possible pain) to avoid enrolling people with uncontrolled pain after surgery. The patient’s pain score after leaving the recovery room needed to increase to more than 4 before the first dose of study drug could be self-administered. At screening, people were excluded who were opioid tolerant (taking a daily dose of more than 15 mg of oral morphine or equivalent); who had documented sleep apnoea or were using supplemental oxygen therapy, or who had a chronic pain condition requiring gabapentanoids, steroids or anti-inflammatory drugs. At randomisation, exclusions also included people with respiratory difficulties or intractable vomiting in the recovery room. About half of participants were 65 years or older (52%), mean age was 64 years (range 19 to 88 years) and mean BMI was 30 kg/m² (range 16 to 54 kg/m²). A greater proportion of participants (65%) were female than male.

- Intervention and comparator: participants were randomised in a 1:1 ratio to receive an administration system dispensing a sublingual 15 microgram sufentanil tablet with a 20-minute lockout period or 1 mg IV morphine sulfate PCA with a 6-minute lockout period for
at least 48 hours. Methodology for treatment allocation was not reported in the paper but the marketing authorisation holder has advised that allocation was concealed (personal communication, Grünenthal Ltd). The baseline characteristics of the investigated patient population were comparable between the groups. Inadequate analgesia was treated using supplemental opioid (2 mg IV morphine bolus), which was allowed in the first 30 minutes of the study drug and not more than once per hour throughout the study. Participants who required additional analgesia beyond this discontinued the study because of inadequate analgesia and could receive any standard analgesic available at the clinical site. Participants who had oxygen saturation levels that could not be maintained at 95% or greater with or without the use of supplemental oxygen, respiratory rate less than 8 breaths per minute or excessive sedation could not use the study drug or supplemental morphine until their vital signs had improved.

- Outcomes: the primary endpoint was patient global assessment (PGA) of the method of pain control at 48 hours. Pain control was measured using a 4-point categorical scale (self-assessed by the patient where 1 is poor and 4 is excellent). Success was defined as the proportion of participants who responded ‘good’ or ‘excellent’ (3 or 4). The pre-specified criteria for non-inferiority was that the lower limit of the 95% confidence intervals (CI) of the difference in success rates (sufentanil sublingual tablet system minus IV PCA morphine) could not be less than −15%. Secondary endpoints included PGA at 24 and 72 hours and healthcare provider global assessments (HPGA) of the method of pain control at these time points. Pain responses were assessed at defined time-points throughout the study using the 11-point numerical rating scale to determine pain intensity (SPID) and a 5-point scale where 0 is no relief and 4 is complete relief to determine pain relief (TOTPAR). To assess the ease of use of the 2 systems (sufentanil administration system compared with IV morphine PCA), validated patient and nurse ease-of-care questionnaires (Harding et al. 2010) were completed (see the background to Jove et al. 2015 and Ringold et al. 2015 for details of the questionnaires). The main analysis of the primary and secondary efficacy endpoints was performed on the mITT population, which included all randomised participants who received at least 1 dose of study medication. Safety assessments included adverse events, continuous oxygen saturation, vital signs, sedation levels and use of concomitant medications. The randomised participants who received at least 1 dose of study drug were included in the safety analysis.

<table>
<thead>
<tr>
<th>Table 2 Summary of RCT comparing the sufentanil sublingual tablet system with IV morphine patient-controlled analgesia (Melson et al. 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sufentanil 15 microgram</strong></td>
</tr>
<tr>
<td>Randomised</td>
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### Efficacy

<table>
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<tr>
<th></th>
<th>n=177</th>
<th>n=180</th>
<th>Treatment difference:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong> percentage of participants with successful PGA scores at 48 hours&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78.5% (139/177) 95% CI 72.5% to 84.6%</td>
<td>65.6% (118/180) 95% CI 58.6% to 72.5%</td>
<td>12.9%, 95% CI 3.7 to 22.1&lt;sup&gt;c&lt;/sup&gt; p=0.007 Non-inferiority criteria achieved (p&lt;0.001)</td>
</tr>
</tbody>
</table>

**Non-inferiority criteria achieved (p<0.001)**

### Selected secondary outcomes:

<table>
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<th>n=177</th>
<th>n=180</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LS mean SPID score at 48 hours (SEM)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>77.9 (8.4) 95% CI 61.4 to 94.5</td>
<td>72.3 (8.1) 95% CI 56.4 to 88.3</td>
<td>0.569</td>
</tr>
<tr>
<td><strong>LS mean TOTPAR score at 48 hours (SEM)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>99.9 (3.5) 95% CI 93.0 to 106.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>91.9 (3.4) 95% CI 85.3 to 98.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.055</td>
</tr>
<tr>
<td>Percentage of participants discontinuing due to inadequate analgesia over 48 hours&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.3% (13/177) 95% CI of difference in proportion 3.5% to 11.2%</td>
<td>8.9% (16/180) 95% CI of difference in proportion 4.8% to 13.1%</td>
<td>No analysis reported</td>
</tr>
<tr>
<td>Mean patient total EOC score (SD)</td>
<td>4.5 (0.5)</td>
<td>4.1 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean nurse total EOC score</td>
<td>n=44 4.3 (0.6)</td>
<td>n=43 3.8 (0.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean patient satisfaction score</td>
<td>4.2 (1.0)</td>
<td>3.8 (1.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean nurse satisfaction score</td>
<td>n=44 3.9 (0.7)</td>
<td>n=43 3.4 (0.6)</td>
<td>&lt;0.001</td>
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### Safety

<table>
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<th></th>
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<th>n=180</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting serious adverse events</td>
<td>1.7% (3/177)</td>
<td>2.8% (5/180)</td>
<td>Not statistically significant</td>
</tr>
</tbody>
</table>
Patients reporting any related adverse events | Not reported by treatment groups | No notable differences reported between treatment groups. No analysis reported
--- | --- | ---
88.8% (317/357) |  | 

Number of patient withdrawals from study due to adverse events | 7.3% (13/177) | 10% (18/180) | No notable differences reported between treatment groups. No analysis reported

Nausea | 42.9% (76/177) | 40.0% (72/180) | Not statistically significant

Vomiting | 13.0% (23/177) | 11.1% (20/180) | Not statistically significant

Constipation | 11.3% (20/177) | 8.3% (15/180) | Not statistically significant

Oxygen saturation decrease <95% | 9.6% (17/177) | 9.4% (17/180) | No analysis reported

Abbreviations: CI, confidence interval; LS, least squares; PGA, patient global assessment; SEM, standard error of the mean; SPID, summed pain intensity difference; TOTPAR, total pain relief, SD, standard deviation, EOC, ease-of-care questionnaire.

a Modified intention-to-treat population: all participants who received at least 1 dose of study medication.

b Results reported and clarified in EPAR. For SPID and TOTPAR results at 48 hours, 3 participants in the IV morphine PCA treatment group were dosed prior to obtaining baseline pain scores and, therefore, were excluded from these analyses.

c Additional data provided by marketing authorisation holder, Grünenthal Ltd (personal communication).

d All participants who received at least 1 dose of study drug.

Clinical effectiveness

*Jove et al. 2015* and *Ringold et al. 2015*

In 2 RCTs, sufentanil was statistically significantly better at reducing pain intensity over 48 hours following elective major surgery compared with placebo (see table 1 above). Treatment differences
for pain intensity scores at 48 hours were 87.6 (95% CI 66.2 to 109.0, p<0.001) following knee and hip replacement (Jove et al. 2015) and 50.0 (95% CI 19.9 to 80.1, p=0.001) after open abdominal surgery (Ringold et al. 2015). However, this outcome is difficult to interpret and the clinical importance of these findings is unclear.

The patient orientated secondary outcomes suggest that sufentanil is a better analgesic than placebo for the management of post-operative pain. For example, there were statistically significantly fewer drop-outs because of inadequate analgesia (14.3% compared with 48.1% of people following hip or knee replacement, p<0.001 and 17.4% compared with 31.6% after open abdominal surgery, p=0.035 for sufentanil and placebo respectively). Additionally, a statistically significantly lower proportion of participants required rescue morphine in the sufentanil group compared with the placebo group. However, half of participants in the sufentanil group in Jove et al. 2015 and a third using sufentanil in Ringold et al. 2015 required supplementary analgesia over the 48 hours immediately following major surgery (50.8% compared with 73.1% of people following hip or knee replacement, p<0.001 and 33.0% compared with 66.7% after open abdominal surgery, p<0.001 for sufentanil and placebo respectively). According to the EPAR, the rates of rescue medication use observed in the 2 RCTs appear comparable or even lower than those observed in double-blind placebo controlled trials with other opioid agents in managing post-surgical pain.

Participants and nurses each rated the overall ease-of-care of the system as greater than 4 on the 0 to 5-point scale in both RCTs, suggesting that the device was easy to use.

**Melson et al. 2014**

In this phase III randomised, open-label, non-inferiority trial, sufentanil was compared with the current standard of care, IV morphine PCA, for the management of acute post-operative pain (see table 2 above). The treatment difference for the proportion of participants reporting successful pain control achieved the pre-defined criteria for non-inferiority of the sufentanil sublingual tablet system compared with morphine at 48 hours (p<0.001, the primary outcome). Sufentanil was also found to be statistically significantly superior to morphine for pain control at 48 hours (78.5% compared with 65.6% respectively, difference 12.9%, p=0.007). Healthcare professionals also reported statistically significantly more successful pain control with sufentanil compared with morphine (p≤0.012 at all time-points). However, the clinical importance of the difference between the 2 treatments for the primary endpoint is difficult to interpret. The EPAR notes that the strength of the endpoint is uncertain because of the subjective nature of the patient assessment, the open-label setting and limitations around the non-inferiority design.
For secondary endpoints, there was no statistically significant difference between sufentanil and morphine for pain intensity (SPID, 77.9 compared with 72.3 respectively, p=0.569) or pain relief (TOTPAR, 99.9 compared with 91.9, p=0.055) over 48 hours. Participant withdrawals because of inadequate analgesia were less frequent in the sufentanil group compared with the morphine group (7.3% compared with 8.9%, no analysis reported). The investigators reported that, although participants in the sufentanil group used more supplemental morphine than those in the IV morphine PCA group (mean 2.6 mg compared with 1.0 mg respectively, p<0.001) the difference of 1.6 mg over 48 hours was not clinically meaningful.

Overall ease-of-care and satisfaction scores were found to be statistically significantly better with sufentanil compared with morphine when rated by both patients and nurses (see table 2 for more information).

**Additional results from the EPAR**

The pain outcomes reported in the studies are difficult to interpret. Therefore, the Committee for Medicinal Products for Human Use (CHMP) requested further responder analyses to be performed to determine the clinical significance of the achieved pain reductions seen with the sufentanil sublingual tablet system in the 3 studies. These analyses were conducted in line with literature recommendations (IMMPACT) for chronic pain trials, that a 30% pain reduction indicates at least moderate clinically important differences and a 50% reduction correlates with substantial improvements.

In the responder analyses for Ringold et al. 2015 and Jove et al. 2015, a 50% pain reduction was reached in 37% and 31% of sufentanil participants in these trials compared with 17.5% and 9.6% of placebo participants. The responder analysis for Melson et al. 2014, comparing sufentanil and morphine, determined there was a similar proportion of clinically relevant 50% pain reduction in both treatment groups (30% and 32% respectively). The CHMP concluded that the pivotal trials provide sufficient evidence of the clinical efficacy of sufentanil sublingual tablet system for managing acute post-operative pain, which is at least comparable to the standard of care using IV morphine PCA.

**Safety and tolerability**

The EPAR states that, during phase II and phase III trials, 685 people were exposed to the 15 microgram dose of sublingual sufentanil using the administration device. In those trials, duration of exposure ranged from 12 hours or more (544 people) up to 72 hours or more (15 people). The proposed UK launch date for this novel sufentanil product is September 2016 and there is currently no post-marketing safety data for the device in this UK clinical setting. However, there is
large experience with sufentanil in other countries outside of the UK, in other pharmaceutical forms and in other indications since its first authorisation in 1978.

The CHMP noted that, when administered intravenously, sufentanil shows a safety profile that is similar to other opioids, and systemic adverse effects are believed to be similar with the sublingual formulation. In placebo-controlled, phase III trials, treatment-related adverse events were experienced by 198 participants (46.2%) in the sufentanil group and 50 participants (30.9%) in the placebo system group. The rate of participants experiencing at least 1 adverse event with the sufentanil sublingual tablet system was generally higher than placebo, but lower than IV morphine PCA. The EPAR concludes that the safety profile of sufentanil sublingual is consistent with other opioids, including IV morphine PCA.

In the phase III, placebo-controlled trials (Jove et al. 2015 and Ringold et al. 2015, see table 1 and 2 above), the most common adverse events were:

- nausea (46.9% in the sufentanil sublingual tablet system group and 36.4% in the placebo group)
- pyrexia (17.7% compared with 11.1%)
- vomiting (11.7% compared with 6.2%)
- headache (8.6% compared with 8.0%)
- oxygen saturation decreased (7.7% compared with 3.1%)
- pruritus (6.8% compared with 0%)
- hypotension (5.6% compared with 3.1%)
- dizziness (5.4% compared with 1.9%)
- anaemia (5.1% compared with 3.1%)
- constipation (5.1% compared with 2.5%), and
- post-operative anaemia (5.1% v compared with 3.1%).

In the phase III trial (Melson et al. 2014), which compared sufentanil sublingual tablet system with IV morphine PCA, the rates of common adverse events were similar between the groups although these results may be subject to bias due to the open-label study design.
Irritation of the oral mucosa is a potential source of adverse events related to sublingual administration. However, local irritation was not reported in any of the trials performed using the sufentanil sublingual tablet system. All potential adverse events, contraindications, and interactions are summarised in the summary of product characteristics for sufentanil.

There were 2 deaths during the clinical development program of the sufentanil sublingual tablet system but both were considered unrelated to treatment (cause not reported in the literature). There were few serious adverse events and all were consistent with opioid treatment and the post-surgical setting. Across all phase II and phase III trials, 6.9% of subjects in the sufentanil sublingual tablet system group, 11.1% in the IV morphine PCA group, and 6.0% in the placebo system group experienced adverse events leading to discontinuation (European public assessment report).

According to the EPAR, sufentanil is given via IV and epidural routes in single doses of up to 30–50 microgram/kg body weight and in 'continuous' doses up to 5 microgram/kg/hour in anaesthesia-settings. It, therefore, notes that an overdose in adults using the sufentanil sublingual tablet system seems highly unlikely. However, there is risk of m misdosing, such as misplaced or dropped tablets. Additionally, the abuse potential of sufentanil is well-characterised.

The EPAR states that the sufentanil sublingual tablet system is designed to decrease the risk of misuse, abuse, and diversion of sufentanil and includes several security features to minimise the risk of intentional tampering and diversion (see the product overview section above for further information on the device features). Nevertheless, the summary of product characteristics advises that the risk of misuse, abuse or diversion should be considered when prescribing or administering sufentanil. People on chronic opioid therapy were excluded from all 3 phase III RCTs (Jove et al. 2015, Melson et al. 2014 and Ringold et al. 2015) and people with a history of alcohol or opioid abuse were excluded from the 2 placebo controlled studies (Jove et al. 2015 and Ringold et al. 2015). Data on using sufentanil sublingually for post-operative pain in these populations are limited. The summary of product characteristics reports that people on chronic opioid therapy or opioid addicts may require higher analgesic doses than the sufentanil sublingual tablet administration device can deliver.

The CHMP recommended that the marketing authorisation for sufentanil sublingual tablet system should be restricted to administration in a hospital setting, by physicians who are experienced in the management of opioid therapy to reduce the risk of diversion and ensure early detection of adverse effects and device failure.
In 2014 the US Federal Drug Administration (FDA) decided not to approve a new drug application for sufentanil sublingual tablet system and to ensure proper use of the device, has requested additional information from the manufacturer before it can reconsider a marketing application. A trial to evaluate the usability and functionality of the sufentanil sublingual tablet system will be enrolling participants from March 2016 (Clinical trial identifier NCT02662764).

The summary of product characteristics recommends that, before use, a healthcare professional should ensure that the patient has been appropriately instructed on how to operate the sufentanil administration device to self-administer tablets as needed to manage their pain post-operatively. Only patients who are able to understand and follow the instructions on operating the device should use sufentanil sublingual tablets. The healthcare professional should consider the ability of the individual to use the device appropriately, taking into account, for example, any visual or cognitive impairment.

Evidence strengths and limitations

The CHMP evaluation of the efficacy and safety data from Jove et al. 2015 and Ringold et al. 2015 identified some methodological weaknesses inherent in the primary endpoint (pain intensity), which favoured the sufentanil arms of the studies. Further sensitivity analyses were performed and a clinically important 50% pain reduction (which is the generally accepted threshold for post-operative pain, Moore et al. 2015), was achieved in over a third of participants taking sufentanil.

The results for pain intensity are reinforced by improvements with sufentanil compared with placebo for other clinically relevant outcomes, such as the number of participant drop-outs due to inadequate analgesia and the proportion of participants requiring rescue analgesia. However, specialists consulted during the development of this evidence summary advised that the rescue analgesia dose (IV bolus of morphine 2 mg) was ungenerous in terms of usual clinical practice and this could have led to more withdrawals, particularly in the placebo group, which may have skewed the benefit in favour of the active treatment arm.

For the 2 placebo-controlled RCTs, the EPAR states that the results for the 72 hour time-point were difficult to interpret because participants could opt either to continue or leave the trial after the 48-hour assessment. The reason for each participant’s decision was not collected; therefore, the estimates for the 72 hour time-point may be unreliable and even biased. The CHMP also reported that the pre-defined analysis of the primary outcome was difficult to interpret. They concluded, however, that the further analyses considering average pain reduction over time
showed a clinically important treatment effect, providing sufficient evidence for efficacy in the post-operative setting (European public assessment report).

In Melson et al. 2014, the sufentanil sublingual tablet system was compared in an open-label study to the current gold standard for post-operative analgesia, IV morphine PCA. This study design may have introduced bias because patients and clinicians were aware of which treatment had been allocated. A double dummy design may have minimised the risk of bias. Specialists consulted during the development of this evidence summary advised that usual UK practice is for a 5 minute IV morphine PCA lockout period, not 6 minutes as per the study design in Melson et al. 2014. Potentially, an extended lockout could lead to an underestimate of the treatment benefit in the IV morphine PCA treatment arm, in relation to usual clinical practice.

The CHMP highlighted additional methodological weaknesses in this study, including lack of justification for the large (15%) non-inferiority margin and the categorical (4-point) primary outcome, which was not sensitive to detect differences between the treatments. The CHMP concluded that, given the open-label, non-inferiority design and the subjective patient assessment for the main outcome, the strength of the primary endpoint remains uncertain. However, because this trial was performed in addition to the 2 double-blind RCTs, and showed non-inferiority and statistically superiority of sufentanil compared with morphine, it was considered acceptable supportive evidence (European public assessment report).

The CHMP considered that the study population was appropriate and sufficient efficacy data was also available for adults aged 65 years or more. It is of note that people with pre-existing chronic pain conditions were excluded from the trials. Consequently, specialists advise that this lack of information for using sufentanil in people with acute pain superimposed on a chronic pain condition may limit the generalisability of the results to this population, particularly as managing post-operative pain is more complex in these circumstances. Further limitations of the data are that the studies were conducted in people undergoing hip, knee and abdominal surgery and that applicability of results to other types of surgery is unclear. In addition the participant population were relatively healthy (American Society of Anaesthesiologists physical status of 1 to 3) so the results are not applicable to sicker people (status 4 and 5).

The CHMP concluded that the safety and efficacy data could not be extrapolated to other acute pain indications, longer duration of treatment or other clinical settings; therefore, the marketing authorisation for the sufentanil sublingual tablet system is restricted to acute moderate to severe post-operative pain in a hospital setting for up to 72 hours (European public assessment report).
Context

Alternative treatments for post-operative pain

Acute pain generally responds well to analgesic medicines such as paracetamol, non-steroidal anti-inflammatory drugs and opioids, and according to the British National Formulary (BNF), a combination of opioid and non-opioid analgesics is used to treat post-operative pain. The EPAR states that morphine is the gold standard treatment for the management of acute post-operative pain.

The Royal College of Anaesthetists’ Faculty of pain medicine guidelines recommend that PCA equipment and infusion devices must be available for post-operative pain relief. The British National Formulary advises that hospital protocols should be consulted for details of PCA to relieve acute post-operative pain.

Costs of alternative treatments for post-operative pain

An administration device containing 40 sufentanil 15 microgram sublingual tablets is expected to be launched in September 2016. The cost of the sufentanil sublingual tablet system is confidential until launch.

Specialists consulted during the development of this evidence summary advised that alternative analgesic treatments would depend on the type of surgery performed. Regional anaesthesia or continuous local anaesthesia catheter techniques are sometimes used in surgery to reduce or avoid the need for opioids. Where opioids are required, specialists advised that the most common approach is to use morphine via a PCA or orally, as considered appropriate.

Oral opioids for post-surgical pain control are administered by a nurse at the request of the patient. Reducing the nursing time required to administer controlled drugs to the patient is a potential advantage of the sufentanil sublingual tablet system over other oral opioids.

Other examples of opioids that are used for post-operative analgesia include fentanyl (PCA), oxycodone (PCA or orally) and diamorphine (PCA).

The cost of opioid analgesia will depend on the preparation chosen, the dosage used (which will differ according to local hospital protocols), any procurement discounts and any administration or other costs incurred. Therefore, it is not possible to provide a comprehensive list of costs for alternative treatments in this evidence summary.
Specialists advised that the usual opioid PCA of choice, morphine, is generally prescribed at a dose of 1 mg/ml in adults, with a 5 minute lockout period. Morphine sulfate 1 mg/ml solution for IV infusion costs £5.25 for a 50 ml vial, excluding VAT and any procurement discounts or other costs incurred, such as administration (BNF, February 2016). If a dose is administered every 5 minutes, 6 vials would be needed over 24 hours, costing £31.50. It is likely that the cost of sufentanil sublingual tablets and the administration device will be significantly more than the current standard of care, for example the cost of IV morphine PCA.

**Estimated impact for the NHS**

**Likely place in therapy**

Although all the studies have methodological limitations, sufentanil has been shown to be better than placebo and comparable to IV morphine PCA for reducing post-operative pain, with an adverse event consistent with other opioids. As with other opioids, it carries a risk of abuse and diversion.

In the studies, participants and healthcare professionals found the sufentanil sublingual tablet system to be user friendly. The EPAR suggests that the sublingual route of administration is a potential benefit of the sufentanil tablet system because it provides an alternative to IV access, avoiding some problems associated with IV administration, such as handling and dosing errors associated with programmable infusion pumps. However, specialists consulted during the development of this evidence summary advised that anyone having major surgery sufficient to need strong opioid analgesia will probably have an IV infusion in situ.

Although IV PCA systems are still used, specialists considered that the use of oral opioids is increasing. Moving away from IV infusions encourages mobility and compliance with physiotherapy goals. The disadvantage of oral opioids is the nursing time required to administer controlled drugs to the patient, especially if multiple breakthrough doses are required. A PCA system for oral opioids mitigates this situation. However, the risks of moving around when taking strong opioids (such as falls) remain whichever mode of analgesia is used.

Specialists advised that the recommendation for the patient not to eat or drink and to minimise talking for 10 minutes post-sufentanil dose may be inconvenient, particularly after the first 24 hours post-surgery. The marketing authorisation for sufentanil sublingual tablet system is limited to the management of post-operative pain for up to 72 hours; therefore, analgesia may potentially have to be altered in patients who need treatment for longer than this.
There is a risk of misdosing with the cartridge device (through lost or dropped tablets or failure of the device) and a potential risk of diversion once the tablet has been dispensed. The summary of product characteristics states that only people who are able to understand and follow the instructions to operate the administration device should use sufentanil sublingual tablets, and that the ability of the patient to use the device appropriately should be taken into consideration by prescribers. For example, the person's cognitive and visual function, and manual dexterity will need to be taken into account. The summary of product characteristics also warns that the potential for abuse should be considered when prescribing or administering sufentanil if there is concern about an increased risk of misuse, abuse or diversion.

There is limited clinical experience with the sufentanil sublingual tablet system. Approximately 700 people used the marketed device in clinical studies. The lack of post-marketing data means that there is uncertainty about any potential unfavourable effects related to this new therapeutic indication for sufentanil, administration as a PCA using the sufentanil system, and taking the sublingual tablet. The EPAR states that the impact of these uncertainties seems to be small; however, as part of the product's risk management plan, educational materials for healthcare professionals provide guidance on appropriate use and minimising risk.

As well as efficacy, safety and individual user factors, local decision makers will need to take cost into account when considering the likely place in therapy of sufentanil and this is unknown until launch. The marketing authorisation holder of sufentanil sublingual tablet system, Grünenthal Ltd, has advised that, as with IV PCA, the administration device (controller) will be costed separately. It is likely that the cost of sufentanil tablets and the controller will be significantly more than the current standard of care, for example the cost of IV morphine PCA.

**Estimated usage**

The marketing authorisation holder of sufentanil sublingual tablets, Grünenthal Ltd, estimates that approximately 2,000 people will be treated with sufentanil in England and Wales in 2016, rising to 67,500 people in 2020. This represents 0.125% and 4.2% of an estimated 1.6 million surgical procedures considered painful enough to require strong opioid use respectively (personal communication, Grünenthal Ltd).

**Relevance to NICE guidance programmes**

There is currently no NICE guidance on managing post-operative pain. Sufentanil was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.
References


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Neetu Bansal, Andrew MacLennan and Catherine Stannard had no interests to declare.

Roger Knaggs has received research funding from Grünenthal Ltd for investigating trends in opioid prescribing and associated outcomes (2012–2015) and research funding from MundiPharma Research for investigating prescription opioid abuse (2015).

About this evidence summary

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.