Application to add certain morphine formulations to the Essential Medicines List for Children

Summary statement of the proposal for inclusion

Pain in children is a public health concern of major significance in most parts of the world. Although the means and knowledge to relieve pain exists, children’s pain is often not recognized, is ignored, or even denied. It is important that adequate access to appropriate formulations of morphine be available for the treatment of moderate to severe persisting pain in children worldwide.

To align the Essential Medicine List for Children (EMLc) with the recently published WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses [WHO pediatric pain guidelines, 2012: p.73 – further referred to as “Guidelines”], it is necessary to add more opioid preparations to the EMLc. These Guidelines consider morphine the strong opioid of first choice to treat moderate and severe pain. Additionally, it is necessary to update the morphine monograph in the Model Formulary in accordance to the aforementioned Guidelines.

With this application, we request:
1. Addition of certain morphine preparations to the EMLc
2. Harmonization of the terminology used for slow-release preparations
3. Modification of the monograph in the WHO Formulary for children

This application is part of a series of three applications:
- Application to add certain morphine formulations to the Essential Medicines List for Children;
- Application to add oxycodone to the Essential Medicines List for Children; and
- Application to add hydromorphone to the Essential Medicines List for Children.

Name of the focal point in WHO submitting or supporting the application

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Name of the organizations consulted and/or supporting the application

Members of the Guidelines Development Group for the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses reviewed the
draft proposal and support it: Dr Allen Finley, Chair of the GDG and Dr John Collins, Member.

**International Nonproprietary Name of the medicine**

Generic name: Morphine sulfate; morphine hydrochloride (No INN available: it is the policy of the INN programme not to select names for those substances that have a long history of use for medical purposes under well-established names such as those of alkaloids (e.g. morphine, codeine), or trivial chemical names (e.g. acetic acid). [International Nonproprietary Names, 2004]

**Preparations proposed for inclusion, including request for harmonization of terminology and proposal for a monograph in the WHO Model Formulary for children**

1. **Addition of morphine preparations to the EMLc:**

**Preparations to be added**

In order to provide adequate pain treatment for persisting pain in children, it is required that the following formulations be added to the Essential Medicine List for Children, under section 2.2 Opioid Analgesics:

- *Granules (slow-release; to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate)*
- *Tablet (slow-release): 100 mg, 200 mg (morphine sulfate or hydrochloride)*

The preparations mentioned under *b.* should be equally added to the palliative care section of the EMLc.

**Rationale for these strengths and dosage forms**

**Introduction**

The WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses identify four key concepts for the correct use of analgesic medicines and three of these concepts affect the need and selection for morphine preparations [Guidelines, 2012: pages 38–40]:

- dosing at regular intervals (“by the clock”)
- using the appropriate route of administration (“by the mouth”)
- tailoring treatment to the individual child (“by the individual”).

The WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children recommend morphine as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses. [Guidelines, 2012: Guideline 5, p. 42]; both slow-release and immediate-release preparations should be available [Guidelines, 2012: Guideline 8, p. 43; Guideline 9, p. 43 ]; and oral administration of opioids is the recommended route of administration. [Guidelines, 2012: Guideline 13, p. 45]. Therefore, the

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* Although morphine hydrochloride is not mentioned in the guidelines, there is no therapeutic difference with morphine sulfate. Slow-release tablets available in trade are prepared using both salts. Also both APIs are available in trade. Therefore, we recommend to include both the sulfate and the hydrochloride salts of morphine for all strengths of the slow-release tablets.
availability of a full range of preparations is essential, including the availability of preparations for slow-release.

**Liquid slow-release dosage form**

Access to multiple strengths of slow-release morphine is essential for the treatment of moderate to severe persisting pain in children as slow-release morphine allows for longer dose intervals, and this improves the patient’s compliance by reducing dose frequency. However, child appropriate dosage formulations for opioids are currently limited to oral liquids, which are often prepared as required by pharmacists. The oral liquids do not have slow-release characteristics, and therefore require frequent administration every four hours, which may be or may not be provided. Older children may be able to swallow slow-release morphine tablets, but young children and infants may only be able to use liquid formulations of morphine. Slow-release tablets cannot be chewed, crushed or cut and are therefore not appropriate for use with children. Slow-release granules, when mixed with water (or apple sauce, for instance) provide access to a "liquid" slow-release formulation.

The pharmacological profile of morphine in the guidelines lists as one of the dosage forms “Granules: (prolonged release, to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).” [Guidelines, 2012: p. 73].

**Need for additional strengths of slow-release morphine**

To obtain a dose that provides adequate relief of pain with an acceptable degree of side-effects, the doses of morphine or other strong opioids need to be gradually increased until effective. Unlike paracetamol and NSAIDs, there is no upper dosage limit for opioid analgesics because there is no "ceiling" analgesic effect. The appropriate dose is the dose that produces pain relief for the individual child. The goal of titration to pain relief is to select a dose that prevents the child from experiencing pain between two doses using the lowest effective dose. This is best achieved by frequent assessment of the child’s pain relief response and adjusting the analgesic doses as necessary.

The opioid dose that effectively relieves pain varies widely between children, and in the same child at different times, and should, therefore, be based on the child's pain severity assessment. Large opioid doses given at frequent intervals may be necessary to control pain in some children; these doses may be regarded as appropriate, provided that the side-effects are minimal or can be managed with other medicines. Therefore, high-end strengths of morphine should be added to the EMLc. [WHO guidelines, 2012: p.41] The pharmacological profile of morphine in the guidelines lists for slow-release tablets “Tablet (prolonged release): 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (as sulfate)” [Guidelines, 2012: p. 73].

2. **Harmonization of nomenclature**

   Additionally, it is requested that a clarification in terminology be made. Currently "controlled-release", "modified-release" and "prolonged-release" are used all three for morphine preparations in the EMLc, in spite that there is not any difference in meaning. “Slow-release” is often used elsewhere. It is preferred that always the same term be used. In preference to controlled-release or modified-release, “slow-release” and “prolonged-release” most clearly define what the preparation does. However, “prolonged-release” can be abridged to “P.R”, which could also be interpreted as “Per recto” and potentially lead to the delivery and administration of unintended dosage forms. Therefore we propose that the term to be used be “slow-release”, as we are not aware of confusing interpretations of its acronym “SR” (at least not in the English language).
3. **Modification of the Morphine Monograph in the WHO Formulary for Children**

The publication of the WHO Guidelines on the pharmacological treatment of persisting pain in children entails also a pharmaceutical profile on morphine, following the monograph format of the WHO Formulary for children. The profile contains updated dosage schedules and instruction for titrating the patient to adequate pain management and for weaning opioids. A proposed text is provided in the section entitled ‘Proposed text for the WHO Model Formulary.’

This text is identical to the pharmaceutical profile for morphine in the Guidelines. It corrects the too high dosing recommended in the current Formulary monograph and it completes the dosing instructions with instructions for titrating and weaning, both essential elements for a safe use of opioid analgesics. [Scholten W, 2012]

The current Formulary mentions also the use of oral morphine solution. However, it does not mention how to prepare such a solution, while in most countries this solution is prepared not on an industrial basis, but by pharmacists. In practice this leads to erroneous preparations in terms of strength, stability and preservation. Therefore, a formula for a stable solution is indispensable. The formula for oral morphine solution that is included in the pharmacist’s brochure on the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses should be included in the WHO Formulary for Children (see Annex 1). We suggest that this will not be part of the monograph itself, but an annex to the Formulary.

The Formulary also provides different monographs for morphine under the pain section and the palliative care section. Such differences are unjustified and the monograph for Morphine in the palliative care section should be identical to the monograph under Morphine as an analgesic.

**International availability – sources, manufacturers and trade names**

Slow-release morphine tablets and granules are available for purchase in many countries, and are usually, but not always, relatively inexpensive. In spite that for good treatment both slow-release (SR) and immediate-release (IR) preparations are required, in some countries, due to commercial reasons, only SR formulations are marketed and in some other countries only IR products.

Slow-release tablets are available both as the sulfate (e.g. Kapanol, Sevredol, MS Contin) and the hydrochloride (e.g. Swiss generic M retard Helvepharm). Both salts are available as active pharmaceutical ingredients.

The AIDS Medicines and Diagnostics Service (AMDS) of the WHO HIV Department published a database with manufacturers of morphine around the world at [http://www.who.int/hiv/amds/ControlledMedicineDatabase.xls](http://www.who.int/hiv/amds/ControlledMedicineDatabase.xls)

**Trade names**

Anamorph, Astramorph, Capros, Duramorph, Kadian, Kapanol, M-long, Morapid, Moscontin, MS Contin, Mundidol, Noceptin, Ordine, Oрапmorph, Roxanol, Sevredol, Skenan, Stellorphine, Vendal and several other brand names [Martindale 32nd Ed., 1999];
Astramorph PF, Chenjen morphine sulfate, Contalgan (–in), Dolcontin, Duramorph PF, Epimorph, Hipnosedan, Infumorph MCR, Mocontin, MS Contin, MSIR, Mundidol, Pectoral, RMS, Roxanol, Statex (morphine sulfate); Hipsedan, MMOS, Modiscop, Morphitec, Mortha, Sedascop, Sédol, Sedospartol, Spasma, Theba-Intran, Vendal (Morphine hydrochloride) and varieties and several other brand names [Multilingual dictionary of narcotic drugs, 1993];


Preparations and manufacturers in some countries
(Dosage forms and strengths as included in this application only)

The Netherlands†
MS Contin 100 mg, tablets Slow Release, Mundipharma
Morfine HCl retard CF 100 mg, tablets Slow Release, Centrafarm
Morfinesulfat retard 100 mg, tablets Slow Release, Pharmachemie
Morfinesulfat Actavis Retard 100 mg, tablets 100mg mg Slow Release, Actavis
Morfine HCl Retard Mylan 100 mg, Tablets Slow Release, Mylan
MS Contin 200 mg, tablets Slow Release, Mundipharma
Morfine HCl retard CF 200 mg, tablets 100 mg Slow Release, Centrafarm
Morfinesulfat retard 200 PCH, tablets 200 mg Slow Release, Pharmachemie
Morfine HCl Retard Mylan 200 mg, Tablets Slow Release, Mylan
Kapanol 20, capsules Slow Release 20 mg, GlaxoSmithKline
Kapanol 50, capsules Slow Release 50 mg, GlaxoSmithKline
Kapanol 100, capsules Slow Release 100 mg, GlaxoSmithKline

Switzerland‡
Kapanol 100, capsules Slow Release 100 mg, GlaxoSmithKline
M retard Helvapharm, Ret Filmtabl 100 mg, Helvapharm
MST Continus, Ret Filmtabl 100 mg, Mundipharma
M retard Helvapharm, Ret Filmtabl 200 mg, Helvapharm
MST Continus, Ret Filmtabl 200 mg, Mundipharma

† Dutch Medicines Evaluation Board database. www.cbg-meb.nl
Sevre Long, Ret Filmtabl 200 mg, Mundipharma

**USA**

Kadian 20mg Capsule, Extended Release, Actavis Elizabeth
Morphine Sulfate 20mg Capsule, Extended Release, Watson Labs
Kadian 30mg Capsule, Extended Release, Actavis Elizabeth
Avinza 30mg Capsule, Extended Release, King Pharmas
Morphine Sulfate 30mg Capsule, Extended Release, Watson Labs
Kadian 60mg Capsule, Extended Release, Actavis Elizabeth
Avinza 60mg Capsule, Extended Release, King Pharmas
Morphine Sulfate 60mg Capsule, Extended Release, Watson Labs
Morphine Sulfate 80mg Capsule, Extended Release, Watson Labs
Kadian Capsule, 100mg Extended Release, Actavis Elizabeth
Morphine Sulfate 100mg Capsule, Extended Release, Watson Labs
Kadian Capsule, 200mg Extended Release, Actavis Elizabeth
Morphine Sulfate 100mg Tablet, Extended Release, Endo Pharmas
Morphine Sulfate 100mg Tablet, Extended Release, Mallinckrodt
Morphine Sulfate 100mg Tablet, Extended Release, Mylan Pharmas Inc
Morine Sulfate 100mg Tablet, Extended Release, Nesher Pharmas
Ms Contin 100mg Tablet, Extended Release, Purdue Pharma Lp
Morphine Sulfate 100mg Tablet, Extended Release, Ranbaxy Labs Ltd
Morphine Sulfate 100mg Tablet, Extended Release, Rhodes Pharmas
Morine Sulfate 200mg Tablet, Extended Release, Endo Pharmas
Morphine Sulfate 200mg Tablet, Extended Release, Mallinckrodt
Morphine Sulfate 200mg Tablet, Extended Release, Mylan Pharmas Inc
Morine Sulfate 200mg Tablet, Extended Release, Nesher Pharmas
Ms Contin 200mg Tablet, Extended Release, Purdue Pharma Lp
Morphine Sulfate 200mg Tablet, Extended Release, Ranbaxy Labs Ltd
Morphine Sulfate 200mg Tablet, Extended Release, Rhodes Pharmas

**Whether listing is requested as an individual medicine or as an example of a therapeutic group**

**Individual**

**Information supporting the public**

From a public-health perspective, currently many patients are without access to essential medicines for pain. WHO policies recommend, and international drug conventions require that countries make medicines controlled under these conventions readily available to those in need. Opioid analgesics like morphine, hydromorphone and oxycodone are among these controlled medicines.

The World Health Organization has a policy to promote the availability of strong opioids in countries whose policies or legislation unduly does not allow access to or availability of strong opioids. [Ensuring balance, 2011: p.5] Inclusion in the EMLc is essential for enhancing this policy and for enhancing the availability of both IR and SR preparations.

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5 FDA Database: [http://www.fda.gov/NewsEvents/ProductsApprovals/default.htm](http://www.fda.gov/NewsEvents/ProductsApprovals/default.htm)
It has been well documented that in most countries of the world, patients do not have adequate access to opioid analgesics. The various barriers are described in the *World Medicines Report* [Milani B and Scholten W, 2011] and in the WHO policy guidelines *Ensuring Balance in National Policies on Controlled Substances, Accessibility and Availability of Controlled Medicines*. [Ensuring balance, 2011: p.5] Legal and policy barriers are important reasons why these medicines are not available in many countries. Seya *et al.* estimate that in 2006 only 464 million people had adequate access to opioid analgesics, and 4.7 billion people had virtually no access [Seya *et al.*, 2011].

The World Health Assembly in its resolution 58.22 “On Cancer prevention and control” (2005), called on WHO to address access to opioid analgesics [Resolution WHA 58.22, 2005]. Other international bodies such as the International Narcotics Control Board (e.g. in a special report on the availability of internationally controlled drugs) [Report of the INCB, 2011] and the UN Commission on Narcotic Drugs, have called for greater access for patients to these medicines.

In addition, the International Association for the Study of Pain adopted the Declaration of Montreal, the Union for International Cancer Control published the World Cancer Declaration and a consortium of 60 international and national organizations initiated by Pallium India launched the Morphine Manifesto. [Declaration of Montreal, 2011; World Cancer Declaration, 2006; a Morphine Manifesto, 2012] All these declarations call for adequate access to pain medicines and treatment of pain worldwide.

**Treatment**  
The treatment recommended by the World Health Organization is published in the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. These guidelines address the pharmacological management of persisting pain in children with medical illnesses. As such, they replace the previous guidelines, Cancer pain relief and palliative care in children, which exclusively covered cancer pain. [Guidelines, 2012: p. 10]. Treatment details in this application are based on the Guidelines on the Pharmacological Treatment of Persisting Pain in Children. For the treatment of pain, no special diagnostics are needed, nor any technical monitoring facilities. Although in certain stages of treatment monitoring of the patient is necessary, this refers to clinical monitoring which could include phone calls or home visits to check on progress, dose tracking, or pulse oximetry and respiratory monitoring in hospital, depending on circumstances. In (very) rare circumstances it might include urine drug testing.

The treatment of pain requires to be preceded by and go together with a regular assessment of the pain with simple pain scales, such as the FPS-R scales. Methods are described in Chapter 2, Evaluation of persisting pain in the paediatric population, of the guidelines. [Guidelines, 2012: p. 26-35]

**Treatment recommendations**

**Dosage:**

| Starting dose for opioid-naive patients: |
| Oral (immediate-release formulation): |
| • infant 1–12 months – 80–200 mcg/kg every 4 hours; |
| • child 1–2 years – 200–400 mcg/kg every 4 hours; |
WHO Access to Controlled Medicines Programme  Morphine application EMLc

- **child 2–12 years** – 200–500 mcg/kg every 4 hours; maximum oral starting dose is 5 mg.

**Oral (slow-release formulation):**
- **child 1–12 years** – initially 200–800 mcg/kg every 12 hours.

**Subcutaneous injection:**
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant or child 6 months–2 years** – 100 mcg/kg every 4 hours;
- **child 2–12 years** – 100–200 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

**IV injection over at least 5 minutes:**
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant or child 6 months–12 years** – 100 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

**IV injection and infusion:**
- **neonate** – initially by *intravenous injection* over at least 5 minutes 25–50 mcg/kg, followed by *continuous intravenous infusion* 5–10 mcg/kg/hr;
- **infant 1–6 months** – initially by *intravenous injection* over at least 5 minutes 100 mcg/kg, followed by *continuous intravenous infusion* 10–30 mcg/kg/hr;
- **infant or child 6 months–12 years** – initially by *intravenous injection* over at least 5 minutes 100–200 mcg/kg, followed by *continuous intravenous infusion* 20–30 mcg/kg/hr.

**Continuous SC infusion:**
- **infant 1–3 months** – 10 mcg/kg/hr;
- **infant or child 3 months–12 years** – 20 mcg/kg/hr.

**Continuation:** after a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% with close monitoring of the patient.

**Dose for breakthrough pain**

**Oral** (*immediate-release formulation, IV injection, or subcutaneous*):
- Additional morphine may be administered as frequently as required, with a maximum of 5–10% of the regular daily baseline morphine dose. If repeated breakthrough doses are required, adjust the regular baseline morphine dose guided by the amount of morphine required for breakthrough pain with a maximum increase of 50% per 24 hours.

The WHO guidelines on the pharmacological treatment of persisting pain in children are evidenced based guidelines, produced using the methods prescribed actually for WHO treatment guidelines. Morphine is considered the first-line strong opioid choice for moderate to severe persisting pain in children. [WHO guidelines, 2012: Guidelines 5, p.42 ]
According to the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, the slow-release formulation of morphine is initially dosed at 200-800 mcg/kg every 12 hours in children aged 1-12 years. Slow release granules are used at the same doses, but are administered after being mixed in water. After the appropriate starting dose, the dosage should be adjusted on an individual basis to the level that it is effective (with no maximum dose, unless further increase is not possible because of untreatable side-effects). The maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100% while monitoring the patient carefully. Common adverse effects of morphine include nausea, vomiting, constipation, lightheadedness, drowsiness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, palpitation, bradycardia, postural hypotension, and miosis. Uncommon adverse effects include respiratory depression (dose-related), tachycardia, and palpitations. Rare adverse effects include syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and anaphylaxis. However, if titrated correctly, most side effects can be avoided.

Opioid weaning can be done safely without posing significant health risk to the patient. From the medical standpoint, weaning opioids should be done slowly by tapering the opioid dose. For short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval. In the case of a long-term therapy protocol, the dose should be reduced not more than 10-20% per week. These pharmacological approaches should be accompanied by measurement of withdrawal symptoms using a scoring system [WHO guidelines, 2012: p.47].

The Guidelines Development Group on the WHO guidelines on the pharmacological treatment of persisting pain in children considered the lack of instruction on how to titrate and how to wean patients on opioids considered a hazard. Therefore this information is considered essential for the Formulary monograph. There is a need for comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use in children with persisting pain due to medical illnesses.

It should be mentioned that the initial dosage is lower than often recommended elsewhere [WHO Model Formulary for Children, 2010: p.24; British National Formulary for Children, 2011: p. 254-255; Scholten W, 2012]. The experts considered dosages recommended elsewhere as not deprived of risk. Also the lack of instruction on how to titrate and how to wean patients on opioids is considered a hazard. Therefore this information is considered essential for the Formulary monograph. There is a need for comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use in children with persisting pain due to medical illnesses.

**Summary of comparative effectiveness in a variety of clinical settings**

The guidelines provide the evidence for its recommendations in a number of GRADE tables [WHO guidelines, 2012: p.104] and the further justification for each recommendation is provided in an annex [WHO guidelines, 2012: p.82]. The guidelines also concluded that more research is needed in order to answer specific questions. The guidelines are based on the best knowledge currently available. See Annex 2 and 3 of the application for detailed information regarding the recommendations in the guidelines. Annex 2 contains GRADE tables regarding morphine and Annex 3 contains background information for the
recommendations. (Please also refer to the GRADE Tables in the parallel applications on oxycodone and hydrocodone preparations.)

For clinical data please refer to Annexes 2 and 3.

**Summary of comparative evidence on safety**

1. **Estimate of total patient exposure to date**

   Morphine was discovered in 1804 by Sertürner and has been used as an analgesic since 1827, when it was commercially sold by Merck. Since, it has been used in innumerable patients and it has been shown to be a safe medicine if used correctly. In 2006, the world used 33.14 tonnes morphine corresponding to 331.4 million DDDs. [Seya et al., unpublished data] The annual consumption by country can be roughly derived from the status of estimates as published by the International Narcotics Control Board at [http://www.incb.org/incb/narcotic_drugs_estimates.html](http://www.incb.org/incb/narcotic_drugs_estimates.html).

2. **Description of adverse effects/reactions**

   **Adverse effects**
   - common – nausea, vomiting, constipation, lightheadedness, drowsiness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, palpitation, bradycardia, postural hypotension, miosis;
   - uncommon – respiratory depression (dose-related), tachycardia, palpitations;
   - rare – syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

   **Interactions with other medicines:**
   - amitriptyline – possibly increased sedation, and it may increase plasma concentration of morphine;
   - chlorpromazine – enhanced sedative and hypotensive effect;
   - ciprofloxacin – manufacturer of ciprofloxacin advises that premedication with morphine (reduced plasma ciprofloxacin concentration) be avoided when ciprofloxacin is used for surgical prophylaxis;
   - diazepam – enhanced sedative effect;
   - haloperidol – enhanced sedative and hypotensive effect;
   - metoclopramide – antagonism of effect of metoclopramide on gastrointestinal activity;
   - naloxone* – precipitates opioid withdrawal symptoms;
   - naltrexone* – precipitates opioid withdrawal symptoms;
   - opioid antagonists/partial agonists – may precipitate opioid withdrawal symptoms;
   - ritonavir* – possibly increases plasma concentration of morphine.

3. **Identification of variation in safety due to health systems and patient factors**

   Unlike codeine, which is a pro-drug, morphine is the active agonist itself. Its main metabolite (morphine-3-glucuronide) has no analgesic activity; another metabolite (morphine-6-glucuronide) has a 50% lower analgesic potency than morphine itself. Individual differences are less than for codeine, but exist. For this reason, the dosage level for morphine needs to be established on an individual base [WHO guidelines, p. 37], guided by
the outcome of regular pain assessment. Provided that morphine is prescribed when indicated, and titrated and weaned according to the guidelines, it has shown to be a safe medicine.

Development of dependence on medical treatment is not well documented and it is assumed that the risk is very limited [Noble, 2008; Minozzi, submitted] and this risk is not a reason not to treat when indicated [Minozzi, submitted]. On theoretical grounds, it is likely that pain patients are less susceptible to opioid dependence than other people. [Niikura, 2010]

There are well-described problems with over-prescribing and diversion in a limited number of countries, although these studies are related to prescription to adults and not to children. Non-medical use carries substantial risks, including overdose and mortality. It should be noted that the extensively reported increase in consumption in the United States has been accompanied by a notable increase in overdose deaths involving prescription opioids [CDC, 2011; CDC, 2012]. While there are insufficient data available to quantify the amounts diverted to non-medical use from various parts of the drug distribution system, it appears there is significant theft, fraud and other unlawful conduct [Inciardi JA et al. 2006; Inciardi JA et al., 2006]. A national population-based survey in the United States found that over 70% of those who have reported using opioids non-medically admitted that they obtained the drug for free from friends or family members or through theft or purchase [SAMSHA, 2011]. Large quantities of prescription opioids have been sold by illegitimate pain clinics and overdose has occurred predominantly in persons obtaining opioids from non-medical sources [CDC, 2011]. In a study of unintentional overdose fatalities in West Virginia, 63.1% of the decedents had used pharmaceuticals with no documented prescriptions, and 55.6% of the decedents were never prescribed opioid analgesics. In addition, 79.3% of the decedents has used multiple substances, both illicit and prescription drugs (“polydrug use”), which might have contributed to their death, and 21.4% of the decedents had controlled medicines prescribed by multiple physicians (“doctor shopping”) [Hall AJ et al., 2008]. This study did not determine, however, whether decedents from the latter group were ‘real’ pain patients, or people seeking drugs for illicit purposes. Another American study, describing 9940 cases of overdose deaths, found 51 cases to whom dosages of 100 mg/day or higher of morphine equivalents were prescribed during the first three months of a prescription episode, showing an increased risk for this group [Dunn KM et al., 2010].

In conclusion, although there is no doubt that some, albeit unknown, level of opioid agonist prescribing and dispensing to pain patients contributes to morbidity and mortality in the USA, many if not most of these tragedies appear to involve opioids that have been diverted or obtained through unlawful activities, including those of non-patients.

4. Summary of comparative safety against comparators

Opioids are the only class of medicines effective for moderate and severe pain, and therefore, there are no comparators outside the class. Within the class of opioid analgesics, there are no outspoken differences in safety with the exception of methadone, because of its kinetics.

Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

1. Range of costs of the proposed medicine

There is a high variation in cost, depending on the country, variation in turnover, required paperwork for controlled medicines etc. In some countries, these medicines are
 unavailable because the mark-up for the pharmacy is that low that it is not worth the effort of the additional paperwork (e.g. Ukraine), in other countries some preparations are expensive (e.g. Mexico), sometimes due to the monopoly of one distributor. Cost start as low as US$ 0.05 per patient per day in Uganda, where oral morphine solution is used.

The cost of slow-release capsules 20, 30, 50, 60, 100 and 120 mg and for slow-release capsules 100 and 200 mg were explored for the Netherlands and Switzerland. **

For the capsules, the cost range from Sfr 1.96 – 4.75 per 100 mg (US$ 2.10 – 5.09) in Switzerland, with the higher strengths being cheaper. In the Netherlands, the cost vary from € 1.19 – 2.06 per 100 mg (US$ 1.54 – 2.66), with the highest strength being the cheapest.

The cost of slow-release tablets range from Sfr 1.83 - 2.38 per 100 mg (US$ 1.96 – 2.54), in Switzerland. On a weight basis this is up to 73% less expensive than lower strengths of the same brands. Slow-release tablets cost in the Netherlands between € 0.55 and € 1.16 per 100 mg (US$ 0.71 - 1.50).

As the Swiss price level for medicines is known to be high, the Swiss prices should be regarded as the upper end of the price range. Among European countries, the Netherlands has relatively low medicines prices.

The Opioid Price Watch Project is led by the International Association for Hospice and Palliative Care (IAHPC) in collaboration with the WHO Access to Controlled Medicines Programme. This Project will result in a global map representing the retail price of opioid medicines throughout and within different countries of the world.

2. Comparative cost-effectiveness presented as range of cost per routine

There is no standard dosage for morphine for adult patients and therefore it is even more difficult to define a standard dosage for a child. The wide variability of prices around the world further confuses the picture. Foley et al. found that the average terminal cancer patient needs 75 mg morphine a day during the last three months of his or her life. [Foley, 2006] This corresponds with a dosage of approximately 40 mg morphine per day for the treatment of a ten year old child with comparable pain.

40 mg of treatment during 30 days, formulated as 20 mg SR capsules, would cost in Switzerland Sfr 45.35 (US$ 48.46; 60 pcs Kapanol Retard Capsules 20 mg) and in the Netherlands it would cost € 24.65 per month (US$ 31.84; 60 Kapanol capsules MGA 20mg).. Higher strengths of these capsules are also available and are less expensive on a weight basis.

Slow-release tablets are less expensive than slow-release capsules, but cannot be administered to children who cannot swallow.

Summary of regulatory status of the medicine in several countries

There is no specific country of origin. Morphine (dating back to 1804) is not a patented substance and preparations may be marketed as generics or under a brand name. Specific slow-release systems may be based on patented methods, but alternative methods of preparing slow-release preparations are freely available as an alternative. These preparations have a market authorization in many countries, including EU countries, the United States, Switzerland and elsewhere.

Morphine is subject to international control under the Single Convention on Narcotic Drugs, 1961. For enabling good access in all countries, the World Health Organization published the policy guidelines Ensuring Balance in National Policies on Controlled Substances, guidance for availability and accessibility of controlled medicines in 2011 [Ensuring Balance, p.4].

Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

The International Pharmacopoeia, the British Pharmacopoeia and the Unites States Pharmacopoeia have all three monographs for morphine sulphate and morphine hydrochloride. In addition, the United States Pharmacopoeia has monographs for morphine extended release tablets and for morphine extended release capsules. [The International Pharmacopoeia, 2011, CD-version; British Pharmacopoeia, 2012, p. 1496; United States Pharmacopoeia, online version accessed 14 September 2012].

Proposed revised text for the WHO Model Formulary††

Morphine

ATC code: N02AA01
Oral liquid: 2 mg (as hydrochloride or sulfate)/ml.
Tablet: 10 mg (as sulfate).
Tablet (slow release): 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (as hydrochloride or sulfate).
Granules: (slow release, to mix with water): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).
Injection: 10 mg (as hydrochloride or sulfate) in 1 ml ampoule.

Indications: moderate to severe persisting pain.

Contraindications: hypersensitivity to opioid agonists or to any component of the formulation; acute respiratory depression; acute asthma; paralytic ileus; concomitant use of, or use within 14 days after ending monoamine oxidase inhibitors; raised intracranial pressure and/or head injury, if ventilation not controlled; coma; use within 24 hours before or after surgery.

†† Proposed monograph identical to the monograph in the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children (page 73 - 76), except that the terminology “slow-release” is used here.
Precautions: impaired respiratory function; avoid rapid injection which may precipitate chest wall rigidity and difficulty with ventilation; bradycardia; asthma; hypotension; shock; obstructive or inflammatory bowel disorders; biliary tract disease; convulsive disorders; hypothyroidism; adrenocortical insufficiency; avoid abrupt withdrawal after prolonged treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis.

Skilled tasks: warn the patient or carer about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike.

Dosage:

**Starting dose for opioid-naive patients:**

**Oral (immediate-release formulation):**
- **infant 1–12 months** – 80–200 mcg/kg every 4 hours;
- **child 1–2 years** – 200–400 mcg/kg every 4 hours;
- **child 2–12 years** – 200–500 mcg/kg every 4 hours; maximum oral starting dose is 5 mg.

**Oral (slow-release formulation):**
- **child 1–12 years** – initially 200–800 mcg/kg every 12 hours.

**Subcutaneous injection:**
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant or child 6 months–2 years** – 100 mcg/kg every 4 hours;
- **child 2–12 years** – 100–200 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

**IV injection over at least 5 minutes:**
- **neonate** – 25–50 mcg/kg every 6 hours;
- **infant 1–6 months** – 100 mcg/kg every 6 hours;
- **infant or child 6 months–12 years** – 100 mcg/kg every 4 hours; maximum starting dose is 2.5 mg.

**IV injection and infusion:**
- **neonate** – initially by *intravenous injection* over at least 5 minutes 25–50 mcg/kg, followed by *continuous intravenous infusion* 5–10 mcg/kg/hr;
- **infant 1–6 months** – initially by *intravenous injection* over at least 5 minutes 100 mcg/kg, followed by *continuous intravenous infusion* 10–30 mcg/kg/hr;
- **infant or child 6 months–12 years** – initially by *intravenous injection* over at least 5 minutes 100–200 mcg/kg, followed by *continuous intravenous infusion* 20–30 mcg/kg/hr.

**Continuous SC infusion:**
- **infant 1–3 months** – 10 mcg/kg/hr;
- **infant or child 3 months–12 years** – 20 mcg/kg/hr.

**Continuation:** after a starting dose according to the dosages above, the dosage should be adjusted to the level that is effective (with no maximum), but the maximum dosage increase is 50% per 24 hours in outpatient settings. Experienced prescribers can increase up to 100%
with close monitoring of the patient.

### Dose for breakthrough pain

**Oral (immediate-release formulation), IV injection, or subcutaneous:**

- Additional morphine may be administered as frequently as required, with a maximum of 5–10% of the regular daily baseline morphine dose. If repeated breakthrough doses are required, adjust the regular baseline morphine dose guided by the amount of morphine required for breakthrough pain with a maximum increase of 50% per 24 hours.

---

**Dosage discontinuation:** after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week (79,80).

**Renal impairment:** mild (GRF 20–50 ml/min or approximate serum creatinine 150–300 micromol/l) to moderate (GFR 10–20 ml/min or serum creatinine 300–700 micromol/l) – reduce dose by 25%; severe (GFR <10 ml/min or serum creatinine >700 micromol/l) – reduce dose by 50% or consider switching to alternative opioid analgesics which have less renal elimination, such as methadone and fentanyl; increased and prolonged effect; increased neurotoxicity.

**Hepatic impairment:** avoid or reduce dose, may precipitate coma.

**Adverse effects:**

- **common** – nausea, vomiting, constipation, lightheadedness, drowsiness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, palpitation, bradycardia, postural hypotension, miosis;
- **uncommon** – respiratory depression (dose-related), tachycardia, palpitations;
- **rare** – syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

**Interactions with other medicines:**

- **amitriptyline** – possibly increased sedation, and it may increase plasma concentration of morphine;
- **chlorpromazine** – enhanced sedative and hypotensive effect;
- **ciprofloxacin** – manufacturer of ciprofloxacin advises that premedication with morphine (reduced plasma ciprofloxacin concentration) be avoided when ciprofloxacin is used for surgical prophylaxis;
- **diazepam** – enhanced sedative effect;
- **haloperidol** – enhanced sedative and hypotensive effect;
- **metoclopramide** – antagonism of effect of metoclopramide on gastrointestinal activity;
- **naloxone** – precipitates opioid withdrawal symptoms;
- **naltrexone** – precipitates opioid withdrawal symptoms;
- **opioid antagonists/partial agonists** – may precipitate opioid withdrawal symptoms;
- **ritonavir** – possibly increases plasma concentration of morphine.
* Indicates severe.

**Notes:**

- Morphine is subject to international control under the Single Convention on Narcotic Drugs, 1961.
- Slow-release morphine preparations must not be crushed or chewed; the child must be able to swallow the whole tablet; alternatively, slow-release granules can be used.
- Subcutaneous injection is not suitable for oedematous patients.
- For continuous intravenous infusion, dilute with glucose 5% or 10% or sodium chloride 0.9%.
- High strength modified-release tablets and capsules should only be used in patients who are opioid tolerant. Administration of these strengths to non-opioid tolerant patients may cause fatal respiratory depression.
- Naloxone is used as an antidote in case of opioid overdose.

**Formula for an oral liquid morphine solution:** please refer to Annex…

**References:**


Hara Y et al. Morphine glucuronosyltransferase activity in human liver microsomes is inhibited by a variety of drugs that are co-administered with morphine. *Drug Metabolism and Pharmacokinetics*, 2007, 22:103–112.


[End of proposed revised text for the WHO Model Formulary]

Acknowledgements

We acknowledge Mrs Margarete Kading for the initial drafting of this application and Dr Catherine Parmiter-Dreiza for converting it into a first draft following the WHO EML application format as published in May 2012.
Annex 1: Proposed text for an Annex to the WHO Model Formulary
[WHO Pharmacists Brochure, 2012]

Formulas for morphine oral solution

In several countries morphine oral solution is used as the standard oral morphine preparation instead of tablets or granules. Considerable savings compared to industrial preparation are made by compounding an oral solution by the pharmacy with morphine sulphate or morphine hydrochloride powder. It will often allow for a better coverage of all patients in need of pain relief with morphine.

However, when selecting a formula for oral morphine solution, the microbiological and physico-chemical stability should be considered. The preservation in particular is important. Several formulas use carcinogenic or ineffective ways of preservation, like bronopol (2-bromo-2-nitropropane-1,3-diol) or chloroform.

WHO recommends using formulas with safe ingredients only, an effective preservation and established microbiological and physico-chemical stability. An example of such a formula is the Morphine Hydrochloride Oral Solution from the Formulary of the Dutch Pharmacists (FNA). A modified version is presented here.

Morphine Hydrochloride Oral Solution FNA (modified)

- **1 mg/ml**
- **5 mg/ml**
- **20 mg/ml**

Courtesy of the Royal Dutch Pharmacists Association (KNMP)

**Declaration**

Active ingredient: 1 mg; 5 mg; 20 mg morphine hydrochloride per ml
Dosage form: oral solution
Excipients: citric acid monohydrate, disodium edetate, methyl parahydroxybenzoate, propylene glycol, purified water

**Formula**

**Strength: 1 mg/ml**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine hydrochloride</td>
<td>100 mg</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>40 mg</td>
</tr>
<tr>
<td>Disodium edetate</td>
<td>100 mg</td>
</tr>
<tr>
<td>Methyl parahydroxybenzoate solution 150 mg/ml FNA‡‡</td>
<td>1.06 g</td>
</tr>
<tr>
<td>Purified water</td>
<td>Add a sufficient quantity to make 100 ml</td>
</tr>
</tbody>
</table>

**Strength: 5 mg/ml**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine hydrochloride</td>
<td>500 mg</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

‡‡ For formula and preparation of Methyl parahydroxybenzoate solution 150 mg/ml FNA see below
Disodium edetate 100 mg
Methyl parahydroxybenzoate solution 150 mg/ml FNA 1.06 g
Purified water Add a sufficient quantity to make 100 ml

**Strength: 20 mg/ml**
Morphine hydrochloride 2 g
Citric acid monohydrate 40 mg
Disodium edetate 100 mg
Methyl parahydroxybenzoate solution 150 mg/ml FNA 1.06 g
Purified water Add a sufficient quantity to make 100 ml

**Preparation**
- Dissolve the morphine hydrochloride in approximately 75 ml of the purified water.
- Dissolve the citric acid monohydrate and the disodium edetate in this solution.
- Add and mix of the methyl parahydroxybenzoate solution 150 mg/ml.

For accuracy reasons, amounts of > 2 ml of the solution are weighed in a dosing or cylindrical beaker, preferably made from plastic or metal. (1 ml 150 mg/ml solution = 1.06 gram). Let the dosing or cylindrical beaker drain completely while mixing well.

Amounts of < 2 ml are measured with the smallest possible syringe (volume of the syringe no more than 2 times the volume to be measured). Add the methyl parahydroxybenzoate solution 150 mg/ml while mixing.

For amounts of liquid greater than 500 ml, it is better to add the methyl parahydroxybenzoate solution gradually while mixing continuously.

- Add a sufficient quantity of purified water to a volume of 100 ml and mix.

**Packaging**
Amber glass bottle for protecting the contents against light.

**Storage**
Either kept in storage bottle or dispensing bottle for patient: store below 25°C; do not store in the refrigerator or freezer; expires in 6 months.

**Quality requirements**
Identity: as stated under the section "Declaration", above.
Content morphine hydrochloride.3H₂O: 90–110% of the declared amount, calculated as the pure substance.

pH: 2.5–3.5.
Appearance: the solution is clear and almost free of visible particles.
Microbiological purity: see Ph. Eur. chapter 5.1.4.
Comment

Formula
Three different strengths allow for individual dosages and if necessary, very high dosages. For reasons of stability, the pH is adjusted to pH 2.5–3.5 \[3\]. This is achieved by the addition of citric acid. In order to protect against further oxidation, disodium edetate is added. This addition is adopted from the formula Viskose Morphinhydrochloridlösung NRF \[4\].

It is recommended to store at room temperature, because it has not been investigated whether morphine crystallizes at lower temperatures.

The solution is preserved with methyl parahydroxybenzoate, which is effective at pH 2.5–3.5.

It is added to the preparation as a concentrated solution (150 mg/ml in propylene glycol). This choice of a concentrated solution is mainly taken because of the safety of the preparer (see below); the potential toxicity of propylene glycol is taken into account.

The taste can be corrected if desired by the addition of flavouring, for example vanilla-coconut essence (2 drops per 100 ml) and 24 g sucrose syrup 63% m/m solution. The amount of concentrated methyl parahydroxybenzoate solution 150mg/ml needs to be reduced proportionally, if the sucrose syrup is preserved with methyl parahydroxybenzoate, in order to obtain an end concentration of methyl parahydroxybenzoate of 1.5 mg/ml in the resulting morphine oral solution.

Rationale for the choice to use methyl parahydroxybenzoate as a solution
Using methyl parahydroxybenzoate as a substance requires dissolving in boiling water. Dissolving in boiling water promotes the microbiological purity of the water, but is less advisable because there is a risk of boiling retardation and unexpected breaking of glass utensils. Therefore, the addition of concentrated solution is preferable. When the water used for the morphine solution is not completely microbiologically safe and has to be boiled anyway, then the method to dissolve methyl parahydroxybenzoate in boiling water can also be used.

Storage
Morphine hydrochloride decomposes in aqueous solutions by oxidation into pseudomorphine and morphine-N-oxide \[3\]. Stability testing of morphine hydrochloride solutions of 35 mg/ml stored in completely filled bottles for 24 months at room temperature has shown no content decrease. However, a discolouration of the solution occurs before the morphine hydrochloride content drops below the 90% limit. The level of discolouration after storing for 12 months is not significant when decanting; the colour corresponds to colour standard BY3 \[5\].

Decomposition under the influence of oxygen (through oxidation) may be accelerated with lower morphine concentrations and in partially filled bottles. The latter occurs in bottles in use by patients. However, this formulation is not subject to this accelerated oxidation, judging from the absence of any appreciable discolouration after 8 weeks. Nevertheless, the shelf life of all strengths of this preparation is limited to 6 months, based on the literature \[3\] and in anticipation of stability testing.
Safety of propylene glycol

When using the concentrated methyl parahydroxybenzoate solution 150mg/ml as indicated, the oral solutions contain 1% propylene glycol. This concentration is particularly relevant when using the solution in children as chronic treatment. For short term use (maximum of 2 weeks), the maximum allowable intake of propylene glycol for children is 200 mg/kg per day. Indications of harmful effects of propylene glycol are described after use of 100 mg/kg per day for children over 13 months [6, 7]. Propylene glycol can be used in amounts up to 25 mg/kg per day according to the United States Food and Drug Administration. However, the Dutch Medicines Evaluation Board CBG (CBG-MEB) is of the opinion that the calculation on which this is based does not apply to propylene glycol; CBG-MEB does not make any statement as to the maximum allowable daily dose for chronic use. For instance, if the limit of 25 mg/kg is used, this would be a maximum of 125 mg (corresponding to 12.5 ml solution) in infants of 5 kg.

In exceptional cases where the 25 mg/kg limit will be exceeded (e.g. neonates with a much lower body weight than 5 kg and in long-term use of multiple preparations preserved with concentrated methyl parahydroxybenzoate solution), it is recommended to omit the preservative and to limit the preparations' shelf life to two weeks stored in the refrigerator.

Concentrated methyl parahydroxybenzoate solution 150 mg/ml FNA

Declaration
Excipients: methyl parahydroxybenzoate, propylene glycol

Formula

Methyl parahydroxybenzoate 15 g
Propylene glycol 91 g

Amounting to 106 g (= 100 ml)

Preparation
Dissolve the methyl parahydroxybenzoate the propylene glycol while gently heating.

Packaging
Bottle

Storage
Bottle.
Store below 25 °C; do not store in the refrigerator or freezer.
Before-use-date (for use in compounding): 24 months after preparation.

Quality requirements
Identity: as stated under the section "Declaration", above.
Content methyl parahydroxybenzoate: 95–105% of the declared amount, calculated as the pure substance.
Appearance: the solution is clear, colourless and nearly without visible particles.
Microbiological purity: see Ph. Eur. chapter 5.1.4.

[End of proposed revised text for the Annex to the WHO Model Formulary]
Annex 2: Pertinent GRADE Tables


### GRADE Table 2

| Author: | Wiffen PJ |
| Date: | 02.12.2008 |
| **Question:** | Should IV morphine PCA vs. IV hydromorphone PCA be used for mucositis pain in children aged approximately 14 years? |
| **Settings:** | Children’s hospital, Boston, MA, USA. |

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td><strong>Efficacy (follow-up: 10–33 days; mean daily pain scores)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
</tr>
<tr>
<td><strong>Adverse events (follow-up: mean 10 days; patient self report)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
</tr>
</tbody>
</table>

IV, intravenous; PCA, patient-controlled analgesia; CI, confidence interval.

<sup>1</sup> No statistical difference between mean daily pain scores. Dose potency hydromorphone to morphine estimated at 5:1:1 (usually considered as 7:1).

<sup>2</sup> Only 10 participants – crossover study. Data extracted as reported.

<sup>3</sup> Assessed mucositis pain not cancer pain.
## GRADE Table 3

**Author:** Wiffen PJ  
**Date:** 08-12-2008  
**Question:** Should intranasal fentanyl vs. intravenous morphine be used in acute pain of bone fractures in children aged 7–15 years?  
**Settings:** Children’s Hospital, Australia.  

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>IV morphine</th>
<th>IV morphine</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomized trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious -2(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>33</td>
<td>34</td>
<td>–</td>
<td>Mean difference between the two groups -4 (-16 to 8)(^a)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

### VAS pain intensity score (follow-up: mean 30 minutes; measured with VAS score; range of scores: 1–100; better indicated by lower values)\(^a\)

### Adverse events (follow-up: mean 30 minutes; physician or nurse report)

| 1 | Randomized trial | No serious limitations | No serious inconsistency | Serious -2\(^b\) | No serious imprecision | None | See below\(^c\) | See below\(^d\) | No evaluable data | – | LOW |

|\(^a\)| IV, intravenous; CI, confidence interval; VAS, visual analogue scale.  
|\(^b\)| Intervention is intranasal fentanyl 1.4 mg/kg. Control is IV morphine approx 0.1 mg/kg.  
|\(^c\)| Acute pain study not cancer pain.  
|\(^d\)| Both groups achieved greater than 30 mm reduction in pain VAS score.  
|\(^e\)| Three out of 33 children had a bad taste in mouth after nasal spray, and one vomited on fentanyl. One had a flush at injection site after IV morphine. No other adverse events. |
**GRADE Table 4**

**Author:** Wiffen PJ  
**Date:** 16-04-2009  
**Question:** Should oral transmucosal fentanyl citrate vs. intravenous morphine be used for extremity injury or suspected fracture in children aged 8–18 years?  
**Setting:** Pediatric tertiary care emergency department. Denver, CO, USA.  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td></td>
<td>Oral transmucosal fentanyl</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
</tr>
</tbody>
</table>

IV, Intravenous; CI, confidence interval; ITT, intention to treat.  
¹ Intervention is transmucosal fentanyl 10–15 mcg/kg; control is IV morphine 0.1mg/kg.  
² Reduction in VAS pain intensity greater than 40 mm in morphine IV group and greater than 60 mm in oral transmucosal fentanyl.  
³ Open study, not blinded.  
⁴ Study in acute pain not cancer pain.
**GRADE Table 5** (table excluded during evidence appraisal as not addressing the clinical questions on comparison of strong opioids and route of administration within the scope of these guidelines)

**Author:** Wiffen PJ  
**Date:** 17-04-2009  
**Question:** Should epidural morphine vs. epidural fentanyl or epidural hydromorphone be used for post-operative pain control for orthopaedic surgery in children aged 3–19 years?  
**Settings:** Children’s hospital, Los Angeles, CA, USA.  

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Incertainty</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-operative pain scores (follow-up: mean 30 hours; 5-point VAS scale)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious(^a)</td>
<td>No serious imprecision</td>
<td>Epidural route</td>
<td>30</td>
<td>30</td>
<td>Descriptive data only. Good pain relief achieved, similar in all groups(^b,c)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adverse events (follow-up: mean 30 hours)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious(^d)</td>
<td>No serious imprecision</td>
<td>Epidural route</td>
<td>–</td>
<td>–</td>
<td>Descriptive data only(^e)</td>
<td>–</td>
</tr>
</tbody>
</table>

CI, confidence interval; VAS, visual analogue scale.

\(^a\) Acute post-operative pain: morphine 10 mcg/kg/h; hydromorphone 1 mcg/kg/h; fentanyl 1 mcg/kg/h.

\(^b\) Ninety participants: 30 per group.

\(^c\) All groups reported good to excellent pain relief. No statistically significant difference.

\(^d\) Respiratory depression, somnolence, nausea, vomiting, pruritus and urinary retention, all at greater incidence in morphine group.
### GRADE Table 6

**Author:** Wiffen PJ  
**Date:** 17-04-2009  
**Question:** Should morphine vs. buprenorphine be used for post-operative pain after orthopaedic surgery in children aged 6 months to 14 years?  
**Settings:** Children’s hospital, Helsinki, Finland.  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td>2 Randomized trials</td>
<td>No serious limitations</td>
</tr>
</tbody>
</table>

**Pain intensity (follow-up: 1–3 days; 10-point CATPI by nurses; verbal rating by patient)**

**Adverse events (follow-up: 1–3 days; not clear apart from categorical scale for sedation)**

| 2 Randomized trials | No serious limitations | No serious inconsistency | Serious \(-2^{1}\) | No serious imprecision | None | Descriptive data only\(^{2}\) | – | No evaluable data | – | LOW |

\(IV\), intravenous; CI, confidence interval; CATPI, categorical pain intensity.  
\(^{1}\) Study 1: 24 hours; Study 2: to the morning of the 3rd post-operative day.  
\(^{2}\) Acute post-operative pain study.  
\(^{3}\) Morphine and buprenorphine as analgesics assessed as good or very good in both studies.  
\(^{4}\) Study 1 (morphine 100 or 50 mcg/kg or buprenorphine 3 or 1.5 mcg/kg) both drugs produced marked sedation — no difference between the groups. Study 2A (morphine 100 mcg/kg or buprenorphine 3 mcg/kg). Study 2A and 2B: 33 reports of adverse events in 28 participants on buprenorphine, 19 reports of AEs in 32 participants on morphine. Vomiting: eight reports in participants on buprenorphine, five reports in participants on morphine. Urinary retention: six reports in each group.

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>2</td>
<td>Randomized trials</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious</td>
<td>No serious imprecision</td>
<td>None</td>
<td>Study 2B (32)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CATPI, categorical pain intensity.

*a* Study 2B: IM morphine 150 mcg/kg or sublingual buprenorphine 5–7.1 mcg/kg; both no more than 6 doses in 24 hours.

*b* Study 2B is a continuation of Study 2A in a surgical ward for days 2–4 post-operative.

*c* Acute post-operative pain study.
## GRADE Table 7

**Author:** Wiffen PJ  
**Date:** 17-04-2009  
**Question:** Should morphine PCA vs. ketobemidone PCA be used for post-operative pain in children aged 6–16?  
**Setting:** Children’s hospital, Stockholm, Sweden.  

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Morphine PCA</th>
<th>Ketobemidone PCA</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Randomized trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious -2(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>30</td>
<td>27</td>
<td>No significant difference between groups(^b,c)</td>
<td>–</td>
<td>LOW</td>
</tr>
</tbody>
</table>

**Pain intensity VAS (follow-up: 3–73 hours)**

**Adverse events (follow-up 3–73 hours; different scales, not stated who assessed)**

| 1              | Randomized trial | No serious limitations | No serious inconsistency | Serious -2\(^a\) | No serious imprecision | None | See below\(^d\) | – | – | – | LOW |

---

\(^a\) Acute post-operative pain study.

\(^b\) Morphine PCA: total consumption 17.4 mcg/kg/h; ketobemidone PCA total consumption 16.4 mcg/kg/h.

\(^c\) Both groups achieved reduction in pain VAS scores of > 30 mm each day. No significant difference between the groups.

\(^d\) Both groups experienced nausea, vomiting, itching and over-sedation. No significant difference between the groups.

PAC, patient-controlled analgesia; CI, confidence interval; VAS, visual analogue scale.
**GRADE Table 10**

**Author:** Wiffen PJ  
**Date:** 17-04-2009  
**Question:** Should oral morphine be used for cancer pain in children?  
**Settings:** 18 countries.  

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Immediate-release morphine</th>
<th>Modified-release morphine</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Randomized trials</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>Not calculated</td>
<td>Not calculated</td>
<td>Similar results from both arms(^b)</td>
<td>–</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**Pain relief (follow-up: 4–30 days; validated scales)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Immediate-release morphine</th>
<th>Modified-release morphine</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Randomized trials</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>Data not available by group(^c)</td>
<td>–</td>
<td>No evaluable data(^c)</td>
<td>–</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

\(^a\) All studies conducted in adults: setting 18 countries (11 European, 3 Asia, 2 North America, 2 Oceania).

\(^b\) Studies showed that similar analgesia could be obtained using either modified-release or immediate-release morphine. Total patients: 3615 (54 RCTs).

\(^c\) No data available by group. Approximately 6% of participants (adults) in the studies who received morphine (any type) found the adverse effects intolerable.
**GRADE Table 11**

**Author:** Wiffen P J  
**Date:** 02-12-2008  
**Question:** Should PCA morphine vs. IM morphine be used in post-operative pain in children and adolescents with a mean age of 13 years?  
**Settings:** Children’s hospital, Boston, MA, USA.  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No. of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>Design</td>
<td>Limitations</td>
</tr>
<tr>
<td>1 Randomized trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
</tr>
</tbody>
</table>

**Patient pain scores (follow-up: 48 hours; achieved a VAS pain scale of at least mild pain)**

<table>
<thead>
<tr>
<th>Adverse events (follow-up: mean 48 hours; patient self report and nurse observation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Randomized trial</td>
</tr>
<tr>
<td>No serious limitations</td>
</tr>
<tr>
<td>Descriptive data onlyb</td>
</tr>
</tbody>
</table>

PCA, patient-controlled analgesia; IM, intramuscular; CI, confidence interval; VAS, visual analogue scale; NNT, number needed to treat.

* Study of post-operative orthopaedic pain.

b Only PCA vs. IM data used. A third group included a baseline continuous infusion of morphine. Data excluded for PCA plus as background infusion. Data extracted as reported.

c No respiratory depression in either group. Sedation was less on PCA than on IM. No difference between the two groups in nausea or return to gastrointestinal function. No difference between the two groups in urinary retention.
### GRADE Table 12

**Author:** Wiffen PJ  
**Date:** 15-02-2010
**Question:** Should PCA morphine with background infusion vs. continuous morphine infusion be used for post-operative pain in children?  
**Setting:** Not stated.  

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Summary of findings</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PCA morphine with background infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous morphine infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absolute</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Randomized trial</td>
<td>Serious¹</td>
<td>No serious inconsistency</td>
<td>Serious²</td>
<td>No serious imprecision</td>
<td>None</td>
<td>7/24 (29.2%)³</td>
<td>15/23 (65.2%)³</td>
</tr>
</tbody>
</table>

PCA, patient-controlled analgesia; CI, confidence interval; VASPI, visual analogue scale of pain intensity.

¹ Results are the number of patients who achieved "mild" pain on day 2. Results calculated from article’s Figure 1.
² No details of randomization or allocation concealment provided.
³ Post-operative pain model not chronic pain.
⁴ Doses: PCA morphine bolus of 15 mcg/kg boli every 10 minutes and background of 15 mcg/kg/hr; continuous morphine 20–40 mcg/kg/hr.
**GRADE Table 13**

**Author:** Wilfen PJ  
**Date:** 17-04-2009  
**Question:** Should oral morphine vs. continuous intravenous morphine be used for painful episodes of sickle cell disease in children aged 5–17 years?  
**Settings:** Jacobson study: Children’s hospital, Toronto, ON, Canada.  

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td>1</td>
<td>Randomized trial</td>
</tr>
</tbody>
</table>

**Pain relief based on Oucher scale (measured with: Oucher scale; range of scores: 0–100; better indicated by lower values)**

| 1 | Randomized trial | No serious limitations | No serious inconsistency | Serious | No serious imprecision | None | 27\(^a\) | 29\(^b\) | – | No significant difference | MODERATE |

**Adverse events (non-directed questionnaire used daily)**

| 1 | Randomized trial | No serious limitations | No serious inconsistency | Serious | No serious imprecision | None | Descriptive data only\(^c\) | – | – | MODERATE |

---

\(^a\) Study is for sickle cell crisis – only oral morphine RCT found for acute or cancer pain. Data extracted as reported.  
\(^b\) Oral morphine 1.9 mg/kg every 12 hours.  
\(^c\) Intravenous morphine 0.04 mg/kg every hour.  
\(^d\) Oral morphine group (27 participants) recorded 62 adverse events, 16 “severe intensity events”. Intravenous morphine group (29 participants) recorded 52 adverse events, 19 “severe intensity events”. The definition of “severe intensity” reports is not provided.
Annex 3: Background to the clinical recommendations

Source: Pertinent parts from the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, page 87-91

A2.2.3 Strong opioids essential in pain treatment

Clinical question
In children with persisting pain due to medical illnesses, what are the benefits as compared to the risks (hastening death, developing dependence, respiratory depression, influencing the child's development) of taking regular or intermittent morphine for pain control as compared with a similar group of patients with persisting pain not taking any opioid analgesics?

Recommendation
4. The use of strong opioid analgesics is recommended for the relief of moderate to severe persisting pain in children with medical illnesses.

Strong recommendation, low quality of evidence

Domains and considerations

Quality of evidence
Although, no systematic reviews or randomized control trials were retrieved to guide determination of the balance between the benefits and disadvantages of the use of strong opioids in children, the panel considered indirect evidence from adult chronic non-cancer pain (71).

The panel noted the following statement, which supported the inclusion of morphine in the 2010 EMLc: “Morphine is the strong opioid of choice in moderate to severe pain in children and this is confirmed by a number of consensus guidelines. There is extensive clinical experience of its use in children and its use should be promoted to ensure adequate analgesia as necessary” (72).

Uncertainty: none.

Risks/benefits

Benefits
The efficacy of strong opioids in the relief of pain is well accepted. The panel noted, however, that studies comparing opioids are possible in this age group provided that acceptable and appropriate trial methodology is used.

Risks
Risks associated with severe side-effects and mortality arising from medication errors were considered manageable, although more data on long-term use in children are necessary.

Uncertainty: none

Values and acceptability

In favour
The panel valued access to effective treatment of pain in children.

Against
None

Uncertainty: none.
Cost
Although access to strong opioids is variable, price is not generally a significant barrier for a number of strong opioids.

Uncertainty: none.

Feasibility
Access to strong opioids for medical use remains a challenge worldwide. However, the rational use of opioid analgesics in countries with limited financial and human resources is feasible and recommended.

Uncertainty: none.

Policy agenda
Countries should review, and if necessary, revise their policies and regulations to ensure availability and accessibility of opioid analgesics for the relief of moderate to severe pain in children as provided for in the preamble of the Single Convention on Narcotic Drugs, 1961.

A2.2.4 Choice of strong opioids

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence to support the use of morphine as a gold standard for strong opioids as compared to the use of other strong opioids (in particular fentanyl, hydromorphone, oxycodone and methadone) in order to achieve rapid, effective and safe pain control?

Recommendations
5. Morphine is recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses.
6. There is insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.
7. Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability, including patient-related factors.

Strong recommendations, low quality of evidence

Domains and considerations
Quality of evidence
The panel noted that morphine has been available for a considerable amount of time and that high quality of evidence is unlikely to be available. The second recommendation was based on comparisons between different opioids and routes of administration in acute pain and post-operative pain in children. (Annex 4. Evidence retrieval and appraisal, GRADE tables 2–4, 6, 7). The assessed level of quality of evidence was downgraded because of the differences in conditions treated and duration of treatment.

Uncertainty: yes.

Risks/benefits
Benefits
Morphine is well established as first-line strong opioid.

Risks
Risks are well described and considered to be manageable. Uncertainty: no, for the use of morphine as a first-line opioid analgesic; yes, in relation to the comparative safety and efficacy of different opioids.

**Values and acceptability**

*In favour*
The panel valued access to effective treatment.

*Against*
None

Uncertainty: none.

**Cost**
Morphine is relatively inexpensive, although prolonged-release oral solid forms are more costly.

Uncertainty: none.

**Feasibility**
A wide range of morphine formulations have been already included in the 2010 EMLc:

- **granules, modified release** (to mix with water) – 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
- **injection** – 10 mg (morphine hydrochloride or morphine sulfate) in 1 ml ampoule
- **oral liquid** – 10 mg (morphine hydrochloride or morphine sulfate)/5 ml
- **tablet** – 10 mg (morphine sulfate)
- **tablet (prolonged release)** – 10 mg, 30 mg, 60 mg, 100 mg, 200 mg (morphine sulfate).

Uncertainty: none.

**Research agenda**
Comparative trials of strong opioids, including fentanyl, hydromorphone, oxycodone and methadone, in the treatment of persisting moderate to severe pain in children of all ages with medical illnesses are needed. They should investigate effectiveness, side-effects and feasibility of use in this population.

Child appropriate oral solid dosage forms are needed.

**A2.2.5 Prolonged-release versus immediate-release morphine**

**Clinical question**
In children with persisting pain due to medical illnesses, should prolonged-release morphine be used in preference to immediate-release morphine to achieve and maintain effective and safe pain control?

**Recommendations**

8. It is strongly recommended that immediate-release oral morphine formulations be available for the treatment of persistent pain in children with medical illnesses.

9. It is also recommended that child-appropriate prolonged-release oral dosage forms be available, if affordable.

*Strong recommendations, low quality of evidence*
## Domains and considerations

### Quality of evidence

There is insufficient evidence to support the use of prolonged-release over immediate-release morphine as a sole agent. The only available evidence is in adults (Annex 4, Evidence retrieval and appraisal, GRADE Table 10). The Cochrane review found that, in spite of the relevance of this comparison, only 15 studies of 460 participants compared prolonged-release morphine preparations with immediate-release morphine (115). None of the trials were large, having a median size of 27 participants (age range: 16–73). The results of these trials show that immediate-release and modified-release morphine formulations are equivalent for pain relief. Approximately 6% of participants (adults) in the studies who received morphine (any type) experienced intolerable adverse effects.

Uncertainty: yes, in relation to children since no studies are available in this age group.

### Risks/benefits

**Benefits**
Immediate-release oral morphine needs to be administered more frequently, but it is always necessary in the management of episodic or breakthrough pain.

**Risks**
Adherence to long-term treatment with immediate-release oral morphine may be problematic.

Uncertainty: none.

### Values and acceptability

**In favour**
The panel valued access to immediate-release oral morphine and noted that commercially marketed prolonged-release oral morphine formulations are sometimes the only products available for procurement.

**Against**
None

Uncertainty: none.

### Cost
Immediate-release oral morphine is relatively inexpensive but may not be commercially available in all countries. Morphine powder for extemporaneous preparation may be available, but requires access to pharmacists and suitable diluents, and its compounding may be subject to legal restrictions. The stability of such preparations needs to be investigated.

Uncertainty: none.

### Feasibility
No problem of feasibility, rather affordability for prolonged-release morphine formulation.

Uncertainty: none.

### Research agenda
Research into appropriate formulations for the extemporaneous preparation of oral liquid morphine is needed. Dissemination of available evidence on the preparation of stable extemporaneous formulations is encouraged.
References


Minozzi S, Amato L, Vecchi S, Davoli M. Systematic review on dependence following treatment with opioid analgesics for pain relief. Submitted for publication.


