Application to add hydromorphone 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 opioid medicines 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.78 – further referred to as “Guidelines”], it is necessary to add more opioids to the EMLc. The Guidelines state that if pain severity associated with a medical illness is assessed as moderate or severe, the administration of a strong opioid is necessary. In that case morphine is the medicine of choice, although other strong opioids should be considered and made available to ensure an alternative to morphine in case of intolerable side-effects. It is advised that two or more strong opioids should be available for this purpose, and hydromorphone is one such strong opioid. Thus, it is requested that hydromorphone be added to the EMLc as an example of the opioid class. Accordingly, it is necessary to add the hydromorphone monograph in the Model Formulary in accordance to the aforementioned Guidelines.

With this application, we request:
1. Addition of hydromorphone as an example of the opioid class to the EMLc
2. Addition of a monograph on hydromorphone 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

Dr. Willem Scholten, Team Leader, Access to Controlled Medicines, Medicines Access and Rational Use, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland. Email address:

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wk.scholten@bluewin.ch (from 1 November 2012)

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1 Two or more alternatives to morphine should be available and this should be expressed in the EMLc, for example as a footnote to the square box.
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

Hydromorphone INN [INN Cumulative List, 2004]

Formulations proposed for inclusion, including a proposal for a monograph in the WHO Model Formulary for children

Preparations to be added to the EMLc

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

a. Injection (as hydrochloride):
   - 1 mg in 1 ml ampoule,
   - 2 mg in 1 ml ampoule,
   - 4 mg in 1 ml ampoule,
   - 10 mg in 1 ml ampoule
b. Tablet: 2 mg, 4 mg, 8 mg (as hydrochloride).
c. Oral liquid: 1 mg (as hydrochloride)/ml.

These preparations 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 hydromorphone 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”).

In relation to this, the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children strongly recommend switching opioids (and/or route of administration) in children in the presence of inadequate analgesic effect with intolerable side-effects. [Guidelines, 2012: Guidelines 10, p. 44] and alternative opioids and/or dosage forms as an alternative to oral morphine should be available to practitioners, in addition to morphine, if possible. [Guidelines, 2012: Guidelines 11, p. 44; 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 availability of a full range of preparations is essential.
Need for a range of strengths of injections

The subcutaneous route (via continuous infusion or intermittent bolus through an indwelling catheter) is widely used and could be a valuable alternative to oral dosages. It is essential that hydromorphone, injection formulation, be available for the adequate treatment of persisting pain in children. Hydromorphone, is more widely available for parenteral administration than oxycodone.

In addition to the more common or traditional ways of administering, patient-controlled analgesia (PCA) is a possible approach to intravenous or subcutaneous administration. It allows children from approximately the age of seven to self-administer "rescue" doses of analgesics for breakthrough pain. A pre-set dose is delivered into an infusion line by a computer-driven pump. For safety, there is a limited lock-out period after each dose so that additional doses cannot be delivered before a specified time has elapsed. Patient-controlled analgesia may be used alone or with concurrent continuous infusions. It should be noted that PCA techniques might require access to expensive equipment.

Need for a range of strengths of immediate release tablets

To obtain a dose that provides adequate relief of pain with an acceptable degree of side-effects the doses of hydrocodone 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, a range of strengths of hydromorphone, as an example of an alternative to morphine, should be added to the EMLc.

[WHO guidelines, p.47]

Need for liquid formulation

The oral administration is the preferred route of administration. Older children may be able to swallow regular or slow-release oxycodone tablets/capsules, but young children and infants may only be able to use liquid formulations of hydromorphone.

Relation to the application for oxycodone

For patients who do not react well to morphine, the guidelines require that two or more alternatives to morphine are available. While morphine has a very wide range of preparations for both oral and parenteral administration and for immediate-release and slow-release, this is not the case for all other strong opioids. Therefore, oxycodone and hydromorphone were selected as together they have a wider range of administration forms readily available: injections, tablets, slow-release tablets, capsules and oral liquid are all covered by this selection.
Why other strong opioids from the guidelines are not selected to serve as the example of a the class of strong opioids alternative to morphine

-Fentanyl: fentanyl may be expensive in some countries and lozenges may be suitable for breakthrough pain, but less suitable for titrating. Therefore, the range of dosage forms as a whole may be less suitable than for oxycodone and hydromorphone.

-Methadone: the long half-life of methadone makes it more difficult to dose.

International availability - sources, manufacturers and trade names

Hydromorphone hydrochloride as a starting material is out of patent. Hydromorphone tablets, injections and oral solution are available for purchase in a number of countries.

Trade names

Dilaudid, Palladone, Hydrostat IR and several other brand names [Martindale 32nd Ed., 1999];

Algiacton, Assilaudid, Biomorfil, Cofalaudid Cormorphina, Dihydromorfon, Dilauden, Dilocol, Dimorfona, Dimorphid, Dimorphisid, Escolaudol, Hymorphan, Imorphan Laudacon, Laudadin, Laudakon, Lucodon, Morficon, Norlaudon, Novelaudon, Percoral, Procoran, Scolaudol, Semcox 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)

Germany

Dilaudid injection 2 mg, Mundipharma GmbH
Palladon® injekt 2 mg, Mundipharma GmbH
Palladon® injekt 10 mg, Mundipharma GmbH

The Netherlands

Palladon injection 2 mg/ml, 1 ml, solution for injection or infusion, Mundipharma Pharmaceuticals B.V.
Palladon injection 10 mg/ml, 1 ml, solution for injection or infusion, Mundipharma Pharmaceuticals B.V.

Switzerland

Hydromorphoni HCl Steurli, Oral Solution 1mg/ml, 50 ml, Streuli Pharma AG Pharmazeutika

USA

Dilaudid Injection, 1 ml ampoules (1mg/ml), Purdue Pharma
Hydromorphone Hydrochloride Injection 1mg/ml, Hospira

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2 Bfarm Database: http://www.bfarm.de/DE/Arzneimittel/3_nachDerZulassung/zugel_AM/zugel_AM-node.html
3 Dutch Medicines Evaluation Board database, www.cbg-meb.nl
5 FDA Database: http://www.fda.gov/NewsEvents/ProductsApprovals/default.htm
Dilaudid Injection, 1 ml ampoules (2mg/ml), Purdue Pharma
Hydromorphone Hydrochloride Injection 2mg/ml, Hospira
Dilaudid Injection, 1 ml ampoules (4mg/ml) Purdue Pharma,
Hydromorphone Hydrochloride Injection 4mg/ml, Hospira
Dilaudid Injection, 1 ml ampoule (10mg/ml), Purdue Pharma
Hydromorphone Hydrochloride Injection 10mg/ml, Hospira
Hydromorphone Hydrochloride Injection 10mg/ml, Barr
Hydromorphone Hydrochloride Injection 10mg/ml, Akorn
Dilaudid tablets, 2mg, Purdue Pharma
Hydromorphone Hydrochloride Tablets USP, 2 mg, Mallinckrodt Inc.
Hydromorphone Hydrochloride Tablets USP, 2 mg, Lannet
Dilaudid tablets, 4mg, Purdue Pharma
Hydromorphone Hydrochloride Tablets USP, 4 mg, Mallinckrodt Inc.
Hydromorphone Hydrochloride Tablets USP, 4 mg, Lannet
Dilaudid tablets, 8mg, Purdue Pharma
Hydromorphone Hydrochloride Tablets USP, 8 mg, Lannet
Hydromorphone Hydrochloride Tablets USP, 8 mg, Elite Labs
Hydromorphone Hydrochloride Tablets USP, 8 mg, Tagi Pharma
Dilaudid Oral Solution, 5mg/5ml, Purdue Pharma,
Hydromorphone Hydrochloride Oral Solution, 5mg/5ml, Roxane

It should be noted from this listing that also in industrialized countries the availability of appropriate paediatric formulations for immediate release is often deficient.

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

Listing is requested as an example of a therapeutic group. According to the Guidelines, “alternative opioids” (i.e. two or more alternatives) to morphine should be available and this should be expressed in the EMLc, for example as a footnote to the square box. [Guidelines, 2012: p. 44] The footnote could read “Examples for alternative opioids for morphine. Two or more alternatives should be available in addition to morphine.”

**Information supporting the public health relevance**

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, hydrocodone 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 or availability to strong opioids [Ensuring balance, p.5]. Inclusion in the EMLc is essential for enhancing this policy.

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:**

<table>
<thead>
<tr>
<th>Oral (using immediate-release formulations):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• child – initially 30 – 80 mcg/kg per dose (maximum 2 mg per dose) every 3–4 hours.</td>
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</table>

<table>
<thead>
<tr>
<th>Subcutaneous or intravenous:</th>
</tr>
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<tbody>
<tr>
<td>• child – initially 15 mcg/kg per dose slowly over at least 2–3 minutes every 3–6 hours.</td>
</tr>
</tbody>
</table>

**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.

The WHO guidelines on the pharmacological treatment of persisting pain in children are evidence-based guidelines, produced using the methods prescribed actually for WHO treatment guidelines. Hydromorphone is considered an example of a strong opioid, as an alternative to morphine, for moderate to severe persisting pain in children. Two or more alternatives to morphine should be available and this should be expressed in the EMLc, for example as a footnote to the square box.

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 1 and 2 of the application for detailed information regarding the recommendations in the guidelines. Annex 1 contains GRADE tables regarding morphine and Annex 2 contains background information for the recommendations. (Please also refer to the GRADE Tables in the parallel applications on morphine and oxycodone preparations.)

According to the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, the oral formulation of hydromorphone is initially dosed at 30-80 mcg/kg every 3-4 hours for children. The subcutaneous or intravenous formulation of hydromorphone is initially dosed at 15 mcg/kg over at least 2-3 minutes every 3-6 hours in children. 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 hydromorphone include nausea, vomiting, constipation, dry mouth, sedation, biliary spasm, respiratory depression, muscle rigidity, apnoea, myoclonic movements, asthenia, dizziness, confusion, dysphoria, euphoria, lightheadedness, pruritus, rash, somnolence, and sweating. Uncommon adverse effects include hypotension, hypertension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, miosis, visual disturbances, abdominal cramps, anorexia, paraesthesia, malaise, agitation, tremor, muscle weakness, hallucinations, vertigo, mood changes, dependence, drowsiness, anxiety, sleep disturbances, headache, taste disturbance, agitation, urinary retention, laryngospasm, and bronchospasm. Rare adverse effects include circulatory depression, cardiac arrest, respiratory arrest, shock, paralytic ileus, and seizures. 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, 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 is considered a hazard. [Scholten W, 2012 ] 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. Hydromorphone is considered an example of a strong opioid choice, as an alternative to morphine, for moderate to severe persisting pain in children. Two or more alternatives to morphine should be available and this should be expressed in the EMLc, for example as a footnote to the square box.

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 1 and 2 of the application for detailed information regarding the recommendations in the guidelines. Annex 1 contains GRADE tables regarding morphine and Annex 2 contains background information for the recommendations. (Please also refer to the GRADE Tables in the parallel applications on morphine and oxycodone preparations.)

For clinical data please refer to Annexes 1 and 2.

**Summary of comparative evidence on safety**

1. **Estimate of total patient exposure to date**
   
   Hydromorphone has been used as an analgesic since 1926. Since, it has been used in innumerous patients and it has been shown to be a safe medicine if used correctly. In 2006 the world used 10.2 tonnes hydrocodone or 510 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, dry mouth, sedation, biliary spasm, respiratory depression, muscle rigidity, apnoea, myoclonic movements, asthenia, dizziness, confusion, dysphoria, euphoria, lightheadedness, pruritus, rash, somnolence, sweating;
- uncommon – hypotension, hypertension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, miosis, visual disturbances, abdominal cramps, anorexia, paraesthesia, malaise, agitation, tremor, muscle weakness, hallucinations, vertigo, mood changes, dependence, drowsiness, anxiety, sleep disturbances, headache, taste disturbance, agitation, urinary retention, laryngospasm, bronchospasm;
- rare – circulatory depression, cardiac arrest, respiratory arrest, shock, paralytic ileus, seizures.

Interactions with other medicines:
- central nervous system depressants – additive or potentiating effects with hydromorphone;
- ethanol* – additive or potentiating effects with hydromorphone, potential fatal interaction (dose dumping) if used with extended-release hydromorphone preparations;
- monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
- naloxone* – precipitates opioid withdrawal symptoms;
- naltrexone* – precipitates opioid withdrawal symptoms;
- opioid antagonists/partial agonists* – may precipitate opioid withdrawal symptoms.

* Indicates severe.

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

Inter-individual differences exist. Like for other opioid analgesics, the dosage level for hydrocodone needs to be established on an individual base [WHO guidelines, 2012: p. 37], guided by the outcome of regular pain assessment. Provided that hydrocodone 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. 2006a; Inciardi JA et al., 2006b]. 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

The cost of 1 ampoule of 2mg/ml, 1 ml is € 1.93 (US$ 2.49); that of an ampoule 10mg/ml, 1ml is € 9.67 (US$ 12.51) in the Netherlands. The cost of 50ml oral solution 1mg/ml is in Switzerland Sfr 34,50 (USD 36.95).6

2. Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality adjusted life year gained)

There is no standard dosage for hydromorphone 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 5 mg hydromorphone per day orally (or 2.5 mg per day parenterally) for the treatment of a ten year old child with comparable pain.

If treated with oral solution at the price in Switzerland, one day of treatment costs US$ 3.96; if treated parenterally, at the Dutch price level, the daily cost ranges from US$ 2.99-3.15.

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.

Summary of regulatory status of the medicine in several countries

Hydromorphone was first marketed in Germany in 1926. Currently, it is on the market in Germany, the Netherlands, the United States of America and many other countries, but often in limited ranges of dosage forms and strengths.

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Hydromorphone 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)**


In addition, the United States Pharmacopoeia has monographs on Hydromorphone Hydrochloride oral solution and Hydromorphone Hydrochloride Tablets. [United States Pharmacopoeia, online version accessed 14 September 2012].

**Proposed new text for the WHO Model Formulary**

The publication of the WHO Guidelines on the pharmacological treatment of persisting pain in children entails also a pharmaceutical profile on hydromorphone, 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 below.7

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**Hydromorphone**

**ATC Code:** N02AA03  
**Injection:** 1 mg in 1 ml ampoule, 2 mg in 1 ml ampoule, 4 mg in 1 ml ampoule, 10 mg in 1 ml ampoule (as hydrochloride).  
**Tablet:** 2 mg, 4 mg, 8 mg (as hydrochloride).  
**Oral liquid:** 1 mg (as hydrochloride)/ml.

**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.

**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

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treatment; diabetes mellitus; impaired consciousness; acute pancreatitis; myasthenia gravis; hepatic impairment; renal impairment; toxic psychosis.

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

**Dosage:**

<table>
<thead>
<tr>
<th>Starting dose for opioid-naive patients:</th>
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<tr>
<td><em>Oral (using immediate-release formulations):</em></td>
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<tr>
<td>- child – initially 30 – 80 mcg/kg per dose (maximum 2 mg per dose) every 3–4 hours.</td>
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<td><em>Subcutaneous or intravenous:</em></td>
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<td>- child – initially 15 mcg/kg per dose slowly over at least 2–3 minutes every 3–6 hours.</td>
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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.

**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:** moderate (GFR 10–20ml/min or serum creatinine 300–700 micromol/l) and severe (GFR <10ml/min or serum creatinine >700 micromol/l) – reduce dose, start with lowest dose and titrate according to response.

**Hepatic impairment:** use with caution and reduce initial dose in all degrees of impairment.

**Adverse effects:**

- common – nausea, vomiting, constipation, dry mouth, sedation, biliary spasm, respiratory depression, muscle rigidity, apnoea, myoclonic movements, asthenia, dizziness, confusion, dysphoria, euphoria, lightheadedness, pruritus, rash, somnolence, sweating;
- uncommon – hypotension, hypertension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, miosis, visual disturbances, abdominal cramps, anorexia, paraesthesia, malaise, agitation, tremor, muscle weakness, hallucinations, vertigo, mood changes, dependence, drowsiness, anxiety, sleep disturbances, headache, taste disturbance, agitation, urinary retention, laryngospasm, bronchospasm;
- rare – circulatory depression, cardiac arrest, respiratory arrest, shock, paralytic ileus, seizures.

**Interactions with other medicines:**

- central nervous system depressants – additive or potentiating effects with hydromorphone;
- ethanol* – additive or potentiating effects with hydromorphone, potential fatal interaction (dose dumping) if used with extended-release hydromorphone preparations;
• monoamine oxidase inhibitors* – severe and unpredictable potentiation of opioids;
• naltrexone* – precipitates opioid withdrawal symptoms;
• opioid antagonists/partial agonists* – may precipitate opioid withdrawal symptoms.

* Indicates severe.

Notes:
• Hydromorphone is subject to international control under the Single Convention on Narcotic Drugs, 1961.
• Hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing. Use extreme caution when converting from one route to another.
• Give with food or milk to decrease gastrointestinal upset.
• Extended-release preparations are available; however, these are not indicated for use in the paediatric setting.
• Naloxone is used as an antidote in case of opioid overdose.

Equianalgesic doses:

Hydromorphone - morphine vice versa
According to manufacturers, oral hydromorphone is 7.5 times more potent than morphine; however, when switching from morphine to hydromorphone, some suggest the ratio is 5:1 (i.e. the dose of hydromorphone should be 1/5 of the morphine dose), and when switching from hydromorphone to morphine a ratio of 1:4 should be used (i.e. the morphine dose should be 4 times the hydromorphone dose).

Parenteral hydromorphone to oral hydromorphone
If switching from parenteral to oral hydromorphone, oral doses are less than one-half as effective as parenteral doses (may only be 1/5 as effective). Doses may need to be titrated up to 5 times the IV dose.

References:

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

We acknowledge Mrs Margarette 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: Pertinent GRADE Tables

Pertinent parts from the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, pages 107 and 110.

### GRADE Table 2

**Author:** Wiffen PJ  
**Date:** 02-12-2006  
**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>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 PCA</th>
<th>IV hydromorphone 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>Serious(^a)</td>
<td>No serious inconsistency</td>
<td>Serious(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>10/10 (100%)</td>
<td>10/10 (100%)</td>
<td>No difference</td>
<td>Not pooled</td>
<td>Not pooled</td>
</tr>
</tbody>
</table>

**Efficacy (follow-up: 10–33 days; mean daily pain scores)\(^a\)**

**Adverse events (follow-up: mean 10 days; patient self report)**

<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 PCA</th>
<th>IV hydromorphone 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>Serious(^a)</td>
<td>No serious inconsistency</td>
<td>Serious(^a)</td>
<td>No serious imprecision</td>
<td>None</td>
<td>No data</td>
<td>No data</td>
<td>No statistical difference</td>
<td>–</td>
<td>LOW</td>
</tr>
</tbody>
</table>

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

\(^a\) No statistical difference between mean daily pain scores. Dose potency hydromorphone to morphine estimated at 5:1:1 (usually considered as 7:1).

\(^b\) Only 10 participants – crossover study. Data extracted as reported.

\(^c\) Assessed mucositis 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 patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<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>

CI, confidence interval; VAS, visual analogue scale.

1. Acute post-operative pain: morphine 10 mcg/kg/h; hydromorphone 1 mcg/kg/h; fentanyl 1 mcg/kg/h.
2. Ninety participants: 30 per group.
3. All groups reported good to excellent pain relief. No statistically significant difference.
4. Respiratory depression, somnolence, nausea, vomiting, pruritis and urinary retention, all at greater incidence in morphine group.
Annex 2: Background to the clinical recommendations

Source: Pertinent parts from the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses, pages 87-92.

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

<table>
<thead>
<tr>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risks/benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Risks</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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, 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.
A2.2.6 Opioid rotation and opioid switching

Clinical question
In children with persisting pain due to medical illnesses, what is the evidence to support opioid rotation policies to prevent dose escalation and side-effects?

Recommendations
10. Switching opioids and/or route of administration in children is strongly recommended in the presence of inadequate analgesic effect with intolerable side-effects.
11. Alternative opioids and/or dosage forms as an alternative to oral morphine should be available to practitioners, in addition to morphine, if possible.
12. Routine rotation of opioids is not recommended.

Strong recommendations, low quality of evidence

Domains and considerations

Quality of evidence
No systematic reviews or randomized control trials were found in children. A Cochrane Review exclusively looked for and found no RCTs on opioid switching or rotation in adults and children. Identified case reports, uncontrolled and retrospective studies were examined in order to determine the current level of evidence (116). The review concluded that although for patients suffering chronic cancer pain opioid switching may be the only option for enhancing pain relief and minimizing opioid toxicity, there is a current lack of an evidence base for this therapeutic strategy. A systematic review published in 2006 (117), identified one retrospective study of opioid switching in 22 children with cancer pain. This review described a positive response to switching in patients intolerant to a particular opioid, but noted that RCTs are lacking and that the observations were based on uncontrolled data. Uncertainty: yes, in relation to the potential utility of rotation policies; no, in relation to switching of opioid and/or route of administration in the presence of inadequate effect or intolerable side-effects.

Risks/benefits

Benefits
The panel placed a high value on effective use of adequate doses of the chosen opioid.

Risks
Risks are well described and considered to be manageable. Access to age-appropriate dose conversion table for different opioids is necessary for safe switching.

Uncertainty: none.

Values and acceptability

In favour
The panel placed high value on treating rather than not treating pain and providing an alternative when response is inadequate and side-effects are intolerable.

Against
None

Uncertainty: none.
### Cost
Alternative opioids to morphine might be more expensive. However, there are regional variations in costs and some alternatives to morphine may even be cheaper.

*Uncertainty:* none.

### Feasibility
Access to an age-appropriate dose conversion table for different opioids is necessary for safe switching.

*Uncertainty:* yes.

### Policy and research agenda
The panel requests an update of the 2004 Cochrane review on opioid switching, including data from children, if available. Opioid rotation policies lend themselves to investigation by prospective trials. Such research is encouraged. Research on dose conversion in different age groups is necessary.
References


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


