(1) **Does the application adequately address the issue of the public health need for the medicine?**

   Yes [X]  No [ ]

Please provide brief details:

Morphine preparations were added on EMLc in 2013, and the public health need was then considered to be adequately addressed. The previous application included detailed data only on oxycodone and hydromorphone, the new application does not provide any new data on oxycodone and hydromorphone already listed in EMLc, or data on any other opiates.

(2) **Have all important studies that you are aware of been included in the application?**

   Yes [ ]  No [X]

Please provide brief comments on any relevant studies that have not been included:

The application contains no new studies published since the submission of the previous application (in 2012)

(3) **Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?**

   Yes [ ]  No [X]

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:

The application contains copies of the previous application (2012) relating to data on oxycodone and hydromorphone, which are currently listed in EMLc as alternatives to morphine (with a footnote indicating that alternatives are limited to hydromorphone and oxycodone). The original application for the 19th Expert Committee proposed the addition of hydromorphone and oxycodone “as an example of a class” and explicitly requested that the Essential Medicines List (and the one for Children) mention that: “Two or more alternatives to morphine should be available” in a non-limiting manner. However, the 2012 application did not provide data on any other opioids than those mentioned previously.
The new application does not provide any evidence of efficacy/effectiveness of any other medicines than oxycodone and hydromorphone, which are already listed in EMLc, but refers to the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses published in 2012.

(4) **Is there evidence of efficacy in diverse settings and/or populations?**

Yes ☐ No ✗

Please provide brief details:

The application includes data on oxycodone and hydromorphone only, which are currently listed in EMLc.

(5) **Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?**

Yes ☐ No ✗

Please provide brief details:

The application includes data on oxycodone and hydromorphone only, which are currently listed in EMLc.

**ADDITIONAL CONSIDERATIONS:**

(6) **Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?**

Yes ✗ No ☐

Please provide brief details:

Most of the class of opiates not currently on the EMLc including those suggested as alternatives in the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses (published in 2012), have complicated pharmacology (e.g. disposition, safety and efficacy), and dosing forms not usually used in children of the EMLc age-group (e.g. transdermal patches) requiring training for the safe, effective and/or appropriate use of the medicine.

(7) **Are there any issues regarding the registration of the medicine by regulatory authorities?** (e.g., recent registration, new indications, off-label use)

Yes ✗ No ☐

Please provide brief details:

Not all of the alternatives in the pharmacological class of opiates are labelled for children, or the registration does not cover the whole age range of the EMLc.
(8) **Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?**

Yes ☐ No ☒

Please provide brief details:

No new medicine named in the proposal. The *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* (2012) includes some alternative opioids (fentanyl and methadone). However, additional alternatives to morphine (classified as strong opioid) include for example buprenorphine, diamorphine (heroin), pethidine and tramadol (examples from BNFc 2014-2015), which are not considered in the Guideline.

(9) **Please comment briefly on issues regarding cost and affordability of this medicine.**

Costs have been considered in the guideline for the medicines it includes.

(10) **Any additional comments?**

The original application for the previous, 19th Expert Committee proposed the addition of hydromorphone and oxycodone “as an example of a class” and explicitly requested that the Essential Medicines List (and the one for Children) mention that: “Two or more alternatives to morphine should be available”. The proposal suggested this should be expressed in the lists for example as a footnote to the square box, without any limiting.

The 19th Expert Committee report (WHO TRS 985, page 9) documents the decision and its rationale:

“The WHO documents advise that two or more opioids should be made available to allow switching of opioids and/or route of administration in children in the presence of inadequate analgesic effect and/or intolerable side-effects. However, the application itself stated that there is a need for comparative trials of opioids in terms of effectiveness, adverse effects and feasibility of use in children with persistent pain due to medical illnesses. No evidence was provided on specific subsets of patients responding to a second opioid when there has been no response to the first. There was also no estimate of the proportion of children who might have a poor response to morphine. The bulk of the evidence presented in relation to both the hydromorphone and oxycodone applications dealt with acute pain in children.

There is high availability of oxycodone (though less of hydromorphone) in high-income countries, with multiple formulations being marketed. However, no listing was provided of the formulations that are available in low- and middle-income countries.
The (19th) Expert Committee recommended that a square box symbol be added to the listing for morphine, with a note that alternatives would be limited to hydromorphone and oxycodone.”

The listing of a medicine in the EMLc with a square box symbol indicates that it is listed as a representative of a pharmacological class, and to indicate similar clinical performance within a pharmacological class. According to the explanation of the EMLc, such a medicine listed with a square box should be the example of the class for which there is the best evidence for effectiveness and safety.

The new application proposes that the limiting of the morphine alternatives to oxycodone and hydromorphone in the EMLc should be removed. The new application contains copies of the previous application (of 2012) and includes no new data. The new application does not provide any evidence of efficacy/effectiveness or safety of any other medicines than oxycodone and hydromorphone, which are already listed in EMLc, but refers to the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses published in 2012.

The new application does not name the alternative opiates (in addition to oxycodone and hydromorphone) that it considers should be covered with the unqualified alternatives to morphine as a representative of the pharmacological class. Additional opiates listed in the WHO Guideline are: fentanyl and methadone. However, the pharmacological class of opiates is broader than what is included in the WHO Guideline. Depending on the source, additional alternatives to morphine (classified as a strong opioid) may also include: buprenorphine, diamorphine (heroin), pethidine and tramadol (examples from BNFc 2014-2015). Many of the substances in the pharmacological class of opiates have complicated pharmacology and may have limited paediatric data (e.g. on disposition, safety and efficacy), and some are available in dosing forms not usually used in children of the EMLc age-range (e.g. transdermal patches), so the opioids are not straightforward interchangeable in children and should be considered individually for inclusion in the EMLc and not just as a pharmacological class.

(11) Please summarise the action you propose the Expert Committee takes.

The 19th Expert Committee may agree with the suggestion that additional opioids are needed to allow switching of opioids and/or route of administration in children in the presence of inadequate analgesic effect and/or intolerable side-effects, as already two alternatives are included in the EMLc. However, before changing the current limitation of the alternative opioids to just oxycodone and hydromorphone, the Committee should request a proposal naming, which opioids should be included as additional alternatives in the EMLc, and the proposal should include appropriate data on available formulations, pharmacokinetics, efficacy/effectiveness and safety of the proposed alternative opiates in the age range of the EMLc (children up to the age of 12 yrs).