# Methadone

Essential medicine status

Section: 2. Medicines for pain and palliative care > 2.2. Opioid analgesics

EMLc | ATC codes: N07BC02

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| **Indication** | Chronic cancer pain ICD11 code: ML00.10 |
| **INN** | Methadone |
| **Medicine type** | Chemical agent |
| **List type** | Complementary For the management of cancer pain |
| **Formulations** | Oral > Liquid: 5 mg per 5 mL (as hydrochloride) ; 10 mg per 5 mL (as hydrochloride) ; 5 mg per mL concentrate for oral liquid (as hydrochloride) ; 10 mg per mL concentrate for oral liquid (as hydrochloride)<br>Oral > Solid: 5 mg (as hydrochloride) ; 10 mg (as hydrochloride) |
| **EML status history** | First added in 2017 (TRS 1006) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic equivalence** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Methadone |
| **DrugBank** | Methadone |

## Expert Committee recommendation

The Expert Committee accepted that there is a need for additional opioid treatment options for cancer pain patients. The Committee considered that methadone can be a suitable inexpensive and widely available treatment alternative to morphine. The Committee noted that countries may require training in the use of methadone and therefore recommended the additional indication of methadone on the complementary list to the EML and a new addition to the complementary list of the EMLc for the treatment of cancer pain.

## Background

Methadone oral liquid is currently included in the EML for use in opioid dependence. Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered as alternatives to morphine under a square box listing.

## Public health relevance

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (1). Pain is a frequent and debilitating feature of cancer, occurring across all phases from diagnosis to palliation (2, 3). It is estimated that 31.8% of patients with cancer are undertreated for pain (4). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries, where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, the strong opioid of choice for management of moderate to severe cancer pain. This application proposed methadone as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients.

## Benefits

Analgesic treatment guidelines often consider morphine and other opioids to be comparable and interchangeable in the treatment of chronic cancer pain, although individual responses to these medicines may vary. A study comparing the analgesic efficacy of oral morphine, oral oxycodone, transdermal fentanyl and transdermal buprenorphine found similar levels of pain relief with the four medicines but varying proportions of patients classified as non-responders or poor responders. In addition, all patients required continuous dose adjustments to achieve good analgesic response, and patients treated with morphine often required switching to alternative opioids. Adverse effects were similar except for CNS effects, which were more common with morphine (5). Compared with morphine, methadone has similar affinity for mu- and kappa-opioid receptors and greater affinity for delta-opioid receptors (6, 7). Unlike morphine, methadone also blocks NMDA (N-methyl-D-aspartate) receptors and inhibits neuronal serotonin and norepinephrine reuptake, thereby inhibiting nociceptive transmission (8, 9). The analgesic effect of methadone is probably mediated by synergistic mechanisms that are different from those of morphine. The pharmacokinetics of methadone differ significantly from those of morphine. Methadone has higher oral bioavailability and protein binding and a longer elimination half-life. It is metabolized primarily in the liver to inactive metabolites whereas morphine is metabolized primarily in the kidney and has active metabolites. Methadone may represent an alternative treatment option to morphine in patients with renal disease. The application presented the findings of a search of the literature published since 2012 on methadone and cancer pain. Randomized controlled trials (RCTs) demonstrated the analgesic benefits of methadone in cancer pain patients who were intolerant to, or had inadequate pain relief from, other strong opioids (10) and in patients with head and neck cancer who were experiencing neuropathic pain and were naive to strong opioids (11). In addition, a series of systematic reviews, published between 2012 and 2016, were identified that investigated methadone for cancer in various circumstances including patients receiving methadone maintenance therapy for opioid addiction, rotation from other opioids, and elderly patients. Most of these systematic reviews determined the level of evidence to be low. In a 2014 systematic review of RCTs of methadone in cancer pain, the authors stated that differences in methodology and study design made it impossible to draw definite conclusions regarding the efficacy or safety of, or rotation strategies for, methadone (12). The application also briefly presents findings from a series of retrospective studies, prospective, open-label studies, observational studies and case reports/series. Heterogeneity in outcome measures, methodology and evaluation tools was noted. A retrospective study on the safety and efficacy of methadone in a palliative care unit in Argentina found methadone to be a preferable first-line treatment for cancer-related pain because of its effectiveness at low cost (13). Compared with other opioids, methadone was associated with less opioid rotation (15% versus 50%) and with a longer time to opioid rotation (20.6 versus 9.0 days). In a prospective, open-label study, efficacy and safety of methadone as second-line opioid therapy were assessed in adults with cancer at a palliative care outpatient clinic (14). After rotation to methadone, pain scores decreased significantly and no increase in opioid toxicity was observed.

## Harms

The pharmacokinetics of methadone are very different from those of morphine and are less predictable, varying widely among individuals. Accumulation occurs with repeated dosing and so adverse effects are delayed over time (15–17). The terminal elimination half-life of methadone varies from 13 to 58 hours (and up to 120 hours in some patients) compared with 3–4 hours for morphine (18). This long half-life makes dose adjustment more difficult with methadone than with morphine, necessitating specialist supervision to establish the optimum dosing regimen. No evidence on pharmacokinetics in children was provided in the application. Methadone is also more likely than morphine to give rise to drug–drug interactions with common cancer treatments because it is metabolized by the cytochrome P-450 enzyme group. Methadone is associated with cardiac toxicities through its effects on cardiac conduction – QTc prolongation, torsades de pointes, ventricular fibrillation (19, 20). However, at clinically effective analgesic doses, methadone dosage and duration were found not to be correlated with QTc prolongation, even in the presence of other risk factors (20).

## Additional evidence

In 1986, methadone was compared with morphine in a 14-day randomized open-label study (21). Analgesic effects were similar, as was the pattern of adverse effects; methadone dose was relatively stable (4–24 mg/day) while a substantial increase in dose was reported in patients given morphine. Similar results were achieved in a subsequent study in the same year (22) and again in a prospective randomized study that compared the analgesic and adverse effects and the doses of methadone with those of morphine

(23). A randomized, double-blind controlled trial compared the effectiveness and safety of methadone and morphine as first-line opioids for cancer pain (24). One hundred and three patients were randomly assigned 1:1 to morphine or methadone. The groups had similar baseline scores for pain, sedation, nausea, confusion and constipation. There was a 56% responder rate in the morphine group for a pain response of 20% and 49% for the methadone group. Methadone did not show superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first-line strong opioid for the treatment of cancer pain, and the authors concluded that methadone had comparable efficacy to morphine with more adverse effects and a higher number of dropouts (40.8% vs 31.5%). These studies, and another randomized trial in 2008 (25), showed methadone to have an analgesic effect comparable, but not superior, to that of morphine, with a similar adverse effect profile. Over time, the opioid escalation index was lower for methadone than for morphine, which may explain the reduced tolerance of methadone with respect to morphine. A 2014 systematic review focused on the role of methadone in pain management in elderly patients (26). Seven articles were identified but none was specific to methadone use in elderly patients with cancer. There are insufficient data on the use of methadone as an analgesic in elderly people with cancer. Two methadone titration methods (stop-and-go and progressive) were compared in patients with cancer-related pain who were intolerant to, or whose pain was inadequately relieved by, Level 3 opioids (10). The primary end-point was the rate of success or failure at Day 4, defined as pain relief and no overdose. Pain relief was obtained in 80% of patients and the rate of success/failure was approximately 40% at Day 4 in both groups. The authors concluded that methadone is an effective and sustainable second-line alternative opioid for the treatment of cancer-related pain and that the two methods of titration are comparable in terms of efficacy and safety. Methadone and fentanyl were compared in a randomized trial of 52 strong-opioid-naive patients with head and neck cancer, pain >4 on the Numerical Rating Scale (NRS) and a neuropathic pain component (11). The primary outcomes were reduction in average pain, clinical success (defined as 50% average pain decrease) and reduction in pain interference. Reduction in NRS was higher with methadone than with fentanyl at 1, 3 and 5 weeks; the difference was significant at weeks 1 and 3 and represented the first evidence of efficacy of methadone versus fentanyl in cancer patients with a neuropathic pain component A 2017 Cochrane systematic review of the effectiveness and tolerability of methadone in cancer pain, published after closure of the EML application period, included six studies with 388 participants (27). This review was an update of one done in 2006. It did not include any studies in children. Heterogeneity in methods and comparisons meant that pooled quantitative synthesis of results was not possible. For the main comparison of methadone with morphine, one study of 103 participants reported better than 20% improvement in pain scores for 75% and 76% of participants, respectively. In another study of 54 participants, all patients reported achieving “no worse than mild pain” (i.e. pain score of 3 or less after treatment) based on mean pain scores. Two studies of 148 participants reported mean scores close to 3. The quality of the evidence was considered to be low, downgraded because of risk of bias (random allocation and allocation concealment unclear, small sample sizes) and imprecision (small sample sizes, wide confidence intervals around estimates of effect). The risk of adverse events (relating to appetite, thirst, somnolence) could not be estimated and the quality of evidence was rated very low, downgraded because of the risk of bias and imprecision (as for efficacy) and also for indirectness, with surrogate measures being used for the outcomes of interest. The authors concluded that, based on low-quality evidence, methadone has similar analgesic benefits to morphine and has a role in the management of cancer pain in adults. They further concluded that morphine and fentanyl may be easier opioids to manage but may be more expensive than methadone in many countries.

## Cost / cost effectiveness

No information regarding costs or cost–effectiveness was provided in the application. The MSH (Management Sciences for Health) International Medical Products Price Guide reports a median unit price for methadone oral solution 5 mg/mL of US$ 0.0210/mL. The median unit price for morphine sulfate 10-mg tablet or capsule is reported as US$ 0.1247 (29). In a cross-sectional study of the global availability and prices of opioids (30), oral methadone was found to be the least expensive of the five opioids studied (morphine, methadone, fentanyl, hydromorphone and oxycodone), with a median price of US$ 0.5 for 30 days of treatment. In comparison, the median price for 30 days treatment with immediate-release oral morphine tablets/capsules was US$ 18.9.

## WHO guidelines

The WHO guidelines for management of cancer pain are currently under review. WHO’s 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (28) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient evidence to support a recommendation of alternative opioids as first choice. The guidelines also recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with

intolerable side-effects (strong recommendation, low-quality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

## Availability

Methadone, like morphine, is subject to international control under the Single Convention on Narcotic Drugs, 1961.

## Other considerations

WHO is currently developing new cancer pain guidelines, which are due for completion late 2017 or early 2018.


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