Reviewer No.1 check list for application for addition: Morphine Modified Release (MMR) tablets 10mg, 30mg and 60mg

(1) Have all important studies that you are aware of been included?  

Yes  No √

The application addresses only the analgesic needs of patients with cancer pain. However, pain is prevalent in many other conditions and diseases such as HIV/AIDS, post traumatic pain, chronic degenerative conditions and others (Breivik, H; Hattori, S; Moulin, Dwight E. Prevalence and impact of chronic pain: a systematic review of epidemiological studies on chronic pain. PAIN, 2005).

It is estimated that 20% of the global population suffers some type of ongoing chronic pain that interferes with the basic activities of daily living, of which the vast majority are in developing countries; with insufficient or no access to pain relief (Gureje, O; Von Korff M; Simon GE; Gater R. Persistent pain and well being: a World Health Organization study in primary care J Am Med Assoc 1998; 280:147-51).

Pain is second only to fever as the most common symptom in ambulatory persons with HIV/AIDS and usually involves several sources at once. The causes include tissue injury from inflammation (including autoimmune responses), infection (e.g., bacterial, syphilitic or tubercular) or neoplasia (lymphoma or sarcoma): so-called nociceptive pain. Nearly half of pain in HIV/AIDS is neuropathic, reflecting injury to the nervous systems.

Oral morphine has proven to be a cost-effective pain medication for the treatment of moderate to severe pain. However, opioid analgesics are not adequately available, particularly in developing countries with limited resource settings, due to ignorance of their medical use, restrictive regulations and pricing issues.

Publications, which include guidelines based on clinical evidence, RCTs or meta analysis on the use of morphine in the treatment of severe pain for other conditions different than cancer, are:


(2) **Is there adequate evidence of efficacy for the proposed use?**

Yes √ No

CR studies demonstrate that patients in MMR regimens show better adherence to treatment, report better comfort with the analgesic treatment, and better night time sleep than patients in MIR regimens.


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

Yes √ No

MMR has been proven effective for the management of pain due to different conditions and in different patient populations (paediatric and elderly). Additional publications on the use of MMR in children and older patients include:


(4) **Are there adverse effects of concern?**

Yes √ No

Adverse effects of the modified release formulation are similar to those for immediate release. The common adverse effects are nausea, vomiting, constipation, drowsiness and confusion. Respiratory depression can occur but is rarely a problem if the drug is
appropriately titrated to manage the pain. Dependence syndrome is a common fear but rarely occurs in practice.

(5) Are there special requirements or training needed for safe/effective use?
   Yes   No  √

It is important that health care workers and people taking these medications are aware that MMR is not immediate release and should therefore not be taken on an ‘as needed’ basis for episodic, incident or end-of-dose pain. MMR tablets must not be chewed, crushed or broken.

(6) Is this product needed to meet the majority health needs of the population?
   Yes  √   No

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes  √   No

Morphine sulphate tablets are registered in virtually all WHO’s Member States. It is listed under international and national control, including the following:

• In the United Kingdom: Schedule II, Class A drug under the Misuse of Drugs Act 1971.
• In the United States: Schedule II drug under the Controlled Substances Act.
• In Canada: Schedule I drug under the Controlled Drugs and Substances Act.
• Internationally, morphine is a Schedule I drug under the Single Convention on Narcotic Drugs (1961).

(8) What action do you propose for the Committee to take?

Add the new formulation to the core list.

(9) Additional comment, if any.

See the proposed text of the WHO Formulary should the committee approve the proposal in Annex 1.
Annex 1

Proposed text for the WHO Formulary

Morphine salts
Drug subject to international control under the Single Convention on Narcotic Drugs (1961)
*Morphine immediate release tablets*,morphine sulfate 10 mg
*Oral solution*, morphine hydrochloride or sulfate 10mg/5 ml
*Injection* (Solution for injection), morphine sulfate 10 mg/ml, 1ml ampoule
*Morphine modified release tablets*, morphine sulfate 10mg, 30mg and 60mg tablets

Uses:
Moderate to Severe pain (acute and chronic); myocardial infarction; acute pulmonary oedema; adjunct during major surgery and postoperative analgesia.
Two different formulations are required to meet the need for rapid effect vs. maintained effect:
- Morphine Immediate Release (MIR) (*injection, immediate release tablet and oral solution*) for dose titration, incident pain, breakthrough pain and cases of unstable pain

Contraindications:

Acute respiratory depression; acute alcoholism; where risk of paralytic ileus; raised intracranial pressure or head injury (interferes with respiration, also affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma

Precautions:

Consistently causes constipation.
Severe withdrawal symptoms if withdrawn abruptly; dose needs to be reduced by 50% of the total daily dose each day if necessary.
In case of overdosing, use naloxone iv (see section XX). The prolonged release of MMR tablets may require multiple doses of naloxone or naloxone infusion.
Reduce dose or avoid in the elderly, debilitated and in patients with renal insufficiency.
Other precautions: hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; renal and hepatic impairment; pregnancy and breastfeeding.
MMR tablets must not be chewed, crushed or broken.
**Dosage** (applies equally to morphine sulfate and hydrochloride salts):

*Acute pulmonary oedema:* by slow intravenous injection (2 mg/minute), 5–10 mg. Reduce dose by half in elderly or debilitated patients.

*Myocardial infarction:* by slow intravenous injection (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary.

*Acute pain:* (Liquid or MIR tablets equivalent dosing)
- **ADULT S:** 5–10 mg every 4 hours
- **INFANT and CHILDREN:** 200 micrograms/kg every 4 hours

*Chronic pain:* by mouth or subcutaneous injection (subcutaneous injection is not suitable for oedematous patients). Start with same dose as in *Acute pain.* Once an appropriate level of analgesia is reached, the regimen can be changed to MMR. There is no ceiling effect with opioids, and the dosage may be increased in small increments titrating the dose continuously.

*To change from MIR to an MMR regimen:* The daily dose of MMR is the same as the total 24 hour dose of MIR (regular and rescue doses) in mg/24 hours. The initial dose of MMR should be at the same time as the final dose of MIR as it takes a number of hours to be effective.

*Rescue doses:* Rescue doses for breakthrough and incident pain while taking MMR should be prescribed with MIR at 10% of the daily morphine dose, given every 2 hours if required. If more than three rescue doses are required within 24 hours, the total daily dosage needs to be revised and incremented by the sum of the daily MIR used, up to a maximum increase of 30% of the daily MMR dose.

*To change from an MMR regimen to MIR:* Determine total daily dose of morphine (regular and breakthrough doses) and divide by 6 (4hr intervals). The MIR should be started 12 hours after the last MMR dose with adequate rescue dosing to cover the transition interval.

Laxative regimens need to be started with the administration of morphine and other opioids. Tolerance never develops for the constipation effect and laxatives need to be consistently used during the whole regimen.
Adverse effects:

Constipation, nausea, anorexia, vomiting (particularly in initial stages), dry mouth; spasm of urinary and biliary tract, bradycardia, tachycardia, palpitations; decreased libido, euphoria, hallucinations; drowsiness, confusion, headache, miosis; rash, urticaria, pruritus, sweating, facial flushing; vertigo, postural hypotension, hypothermia. Patients who require morphine in high doses or for a prolonged time or who develop renal insufficiency may accumulate toxic metabolites and manifest signs of toxicity. Signs of neurotoxicity include hyperalgesia, hallucinations, delirium, somnolence, myoclonus, intractable nausea, and/or pruritus. Larger than appropriate doses produce respiratory depression and hypotension.

Additional Facts:

- Because the active drug is gradually released from MMR tablets, MMR can be taken at 12 or 24-hour intervals, depending on the preparation used. Patients with stable controlled pain achieved with minimal breakthrough dosing are likely candidates for MMR.
- Situations where MMR may need to be discontinued include unstable pain, opioid toxicity, and renal insufficiency.
- The occurrence of opioid dependence syndrome in patients to whom morphine is prescribed is rare. Tolerance and withdrawal symptoms (upon interruption) alone are not sufficient for a diagnosis of dependence syndrome, but other symptoms are also required.
- Despite sufficient evidence that shows that pain can be satisfactorily controlled using relatively simple medication regimens, it continues to be under treated due to several reasons:
  - Inadequate knowledge about pain assessment and its treatment
  - Concerns about possible side effects of morphine
  - Patients’ and physicians’ attitudes, fears, and misconceptions about pain and morphine
  - Misinformation about opioid dependence issues
  - Poorly accessible or unavailable pain management services
  - Improper and misguided regulation by governing agencies.
  - Overly restrictive laws and regulations that interfere with access to treatment