19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for review of medicines used in palliative care

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes. The provided review is well prepared and gives most of the information in a systematic unbiased manner.

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Good quality evidence for rational pharmacotherapy for many of the symptoms is lacking. The primary endpoints of clinical trials do not measure important outcomes for which the medicines are to be used in the care of the terminally ill patients like improvement of fatigue, anxiety, anorexia etc. However, there is experience of wide use and consensus amongst experts for most of the common symptoms experienced by terminally ill patients. The medicines that have been recommended in the application are already listed in the EML, either under palliative care or for some other indication. Hence the safety, cost effectiveness, and wide availability have already been scrutinized. The unique position of the terminally ill patient and the objectives of providing palliative care necessitates that evidence must be viewed in the context of what is widely being used at the moment.

(a) Dexamethasone for anorexia: Corticosteroids have a role in the management of anorexia in palliative care. Dexamethasone has been used in a limited number of studies for anorexia though quality of evidence is only moderate to very low.

(b) Dexamethasone for fatigue: The improvement in fatigue and tiredness seen in a number of studies may be due to an improvement in quality of life. This is not a primary outcome of most of the trials. There is moderate evidence to support the use of dexamethasone for fatigue in terminally ill patients. Expert opinion recommends short term use.

(c) Diazepam and Lorazepam for anxiety: Though benzodiazepines have been used in the treatment of anxiety for a long time, evidence to support their use in the treatment of anxiety associated with terminal illness is limited. There is no clear advantage of one formulation over the other in terms of efficacy and safety.

(d) Docusate sodium, senna and sodium picosulfate for constipation: Stimulant laxatives are medicines of choice for patients on strong opioids. There is no clear advantage of one formulation over the other in terms of efficacy and therefore use is decided by availability and cost.

(e) Haloperidol for delirium: There is good evidence to support the use of haloperidol in patients experiencing agitation and delirium associated with terminal illness.

(f) Amitriptyline and fluoxetine: Both these medicines have been shown to be effective in depression. Both take a long time for the antidepressant activity to become manifest. There is no clear advantage of one over the other. Both are already in the EML.
(g) Loperamide for diarrhoea: The recommendation for use of loperamide in diarrhea is mainly for patients with AIDs related diarrhoea in which it has been proved to be useful. It is in the WHO guidelines for clinical management of HIV infections.

(h) Morphine for dyspnea: Morphine is indicated for treatment of dyspnea in palliative care. Evidence is of good quality.

(i) Metoclopramide for nausea and vomiting: Metoclopramide is the medicine of choice in the treatment of nausea and vomiting in palliative care, where the commonest cause for vomiting is gastric stasis.

(j) Morphine and ibuprofen in pain: Morphine is the analgesic of choice in moderate to severe pain in palliative care. Ibuprofen is useful in bone pain and in mild pain. There is good evidence as well as many consensus guidelines which recommend the use of morphine.

(k) Hyoscine butylbromide for respiratory tract secretions: There is not much evidence to prove that this is superior to placebo.

c. Please provide any additional relevant information with reference

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Not applicable
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on cost been provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   All the medicines proposed in the review are inexpensive. Generic formulations are available for all the medicines that have been proposed.

   c. Please provide any additional relevant information with reference.

   d. Is the product available in several low and middle income countries?
      Yes

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences)
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
All the medicines proposed to be in the EML are on the list of essential medicines for palliative care of the International Association for Hospice and Palliative Care (IAHPC). This is the agency that has prepared the provided review.

Morphine, ibuprofen – in WHO guideline for cancer pain

Morphine – in WHO guideline for dyspnea in terminally ill patients

Loperamide – in diarrhea due to AIDS

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

No

6. Is the proposed product registered by a stringent regulatory authority?
Yes – all the products suggested for inclusion have been registered.

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

1. Dexamethasone should be listed in the EML for palliative care for the management of anorexia. However, there is insufficient evidence for use in fatigue at the moment. It should be included in the following formulations:
   Injection: 4mg/mL in 1-mL ampoule
   Oral liquid: 2mg/5mL
   Tablet: 2mg
   The 2 mg tablet may be retained in the EML instead of including a new strength of 4 mg. This strength will be better served for all weight ranges from very young adults to elderly.

2. Diazepam is should continue to be listed in the EML for anxiety. This is more widely available in many formulations and has a higher therapeutic index. There is no need to add lorazepam to the list as this too belongs to the benzodiazepines. Midazolam may be removed. Diazepam should be included in the following formulations:
   Injection: 5mg/mL
   Oral liquid: 2mg/5mL
   Rectal solution: 2.5mg; 5mg; 10mg
   Tablet: 5mg; 10mg

3. Docusate sodium and senna should continue to be in the list. There is no need to add sodium picosulfate to the list as this does not give any added advantage over senna which is also a stimulant laxative. The two medicines should be included in the following formulations:
   Docusate sodium: Capsule: 100mg; Oral liquid: 50mg/5mL
   Senna: Oral liquid: 7.5mg/5mL

4. Haloperidol should continue to be in the EML for management of delirium in palliative care. It should be included in the following formulations:
   Injection: 5mg in 1-mL ampoule
   Oral liquid: 2mg/mL
   Tablet (immediate release): 10 mg
   Oral solid dosage form: 0.5mg; 2mg; 5mg
5. Amitriptyline and fluoxetine should continue to be in the EML for management of depression in palliative care. The higher strength of amitriptyline (75mg) should also be included. Both these medicines should be included in the following formulations:
   **Amitriptyline:** Tablet: 10 mg; 25 mg; 75 mg
   **Fluoxetine:** Oral solid dosage form: 20mg (as hydrochloride)

6. Loperamide can be included in the EML as there is good evidence of its usefulness in the management of AIDS-related diarrhea it is widely available and cost effective. Loperamide should be included in the EML as oral solid dosage form: 2mg

7. Morphine should be included in the EML for palliative care for pain and dyspnoeoa. There is good evidence and published experience with wide usage. It should be included in the following formulations:
   **Injection:** 10mg/mL
   **Oral liquid:** 10mg/5mL
   **Tablet (immediate release):** 10 mg
   **Tablet (controlled release):** 10mg; 30mg; 60mg

8. Ibuprofen should be included in the EML for management of mild pain and as co-analgesic for bone pain. Ibuprofen should be included in the EML as:
   **Oral liquid:** 200mg/5mL
   **Tablet:** 200mg; 400 mg; 600mg.

9. Metoclopramide should be included in the EML for management of nausea and vomiting in palliative care though there is moderate evidence of its usefulness. It has been widely used and is required for the gastric stasis that is quite common in terminally ill patients. It is easily available and is cost effective. Metoclopramide should be included in the following formulations:
   **Injection:** 5mg/mL in 2-mL ampoule
   **Oral liquid:** 5mg/5mL
   **Tablet:** 10 mg (hydrochloride)

10. Hyoscine butylbromide should not be included in the EML for management of respiratory secretions in the dying phase as there is no evidence to support its use. The provided review states in page 68 that “the patient is unlikely to be aware of, or distressed by accumulated secretions. Management of this symptom is therefore primarily for the benefit of those present in the last hours and days” around the patient.