Expert review No.1
19th Expert Committee on The Selection and Use of Essential
Medicines
April 8-12 2013

Expert peer review on application for AMPHOTERICIN - move from Complementary to Core List.

This application is to change the current listing for amphotericin B from the Complementary List to the Core List. The main indication proposed is for cryptococcal meningitis. This is linked to the publication of a WHO Rapid Advice guideline in 2011, on the diagnosis and treatment of cryptococcal meningitis in patients with HIV. A more complete guideline is apparently in preparation. It is a companion application to the proposal to move flucytosine to the Core list for the same indication.

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes  No (if no, please provide reference and information)
   The application does not provide the evidence summaries that were prepared for the 2011 guidelines; these are available at the website below. The application cites a cost-effectiveness analysis as the basis for the change in listing.

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   The data used for the guideline process is published at:
   The question for this application is the need for special facilities/expertise/ monitoring for safe and effective use of amphotericin. The cost effectiveness analysis uses costs from Uganda, including costs of laboratory monitoring for renal function, with serum electrolytes, over 2 weeks of hospitalization as well as costs of potassium and magnesium supplementation required because of the use of amphotericin. The publication states that
   ‘ the amphotericin based regimens were presumed to require hospitalization for the course of amphotericin along with intensive lab monitoring , IV fluid provision , electrolyte supplementation and 3 LPs”.
   The application does not address the question of whether this constitutes ‘specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training’, which are the criteria for inclusion of a medicine on the Complementary list. For this reviewer, requiring hospitalization etc as specified in the analysis would probably constitute requiring specialized facilities and monitoring.

   c. Please provide any additional relevant information with reference
   NA

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes  No (if no, please provide reference and information)
The application does not provide a comprehensive review of safety, but this has been considered by the WHO Expert Committee previously, when it last reviewed amphotericin.

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

The toxicity of amphotericin is well defined, and includes renal toxicity, fever, rash, nausea and bronchospasm. Avoidance of the renal toxicity in particular requires monitoring of a patient’s renal function and supplementation in some instances with intravenous electrolytes.

c. Please provide any additional relevant information with reference

NA

3. Assessment of cost and availability
a. Have all relevant data on cost been provided

Yes

No (if no, please provide reference and information)

The application provides data on cost and availability of amphotericin.

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)

As noted above, the main evidence used in this application is the cost-effectiveness analysis by Rajasingham et al, in 2012. Notwithstanding the publication of this analysis in a first rank journal, it is badly flawed. The estimates of survival from different treatment regimens are extrapolated from 10 weeks to 1-3 years based on several different cohorts that may or may not be valid for deriving incremental survival benefit, and then assuming ongoing survival benefit over time from treatment. “QALYs” are calculated on the basis of Karnofsky performance scores from patients treated with ART (a completely different intervention) and then the score is applied to the estimated life years. This is not a quality adjusted life year (QALY) - QALYs need to be based on an implied trade-off between survival and quality of life, so a functional status measure of quality of life does not directly translate into a QALY. If anything, this approach is closer to estimating DALYs – but it is not valid for DALYs either. There is no description of the decision analysis used, nor can one see the basis of the probabilistic sensitivity analysis. Not discounting survival is completely incorrect in this context. The results of the analysis cannot be accepted as stated.

c. Please provide any additional relevant information with reference

NA

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)

The application makes the case that in countries with high rates of HIV infection, cryptococcal meningitis is the most common form of meningitis and constitutes a significant public health burden.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

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

YES, as noted above.

6. Is the proposed product registered by a stringent regulatory authority?

   Yes    No

7. Any other comments

The application states: ‘Neither amphotericin nor flucytosine are currently considered WHO Essential Medications [38].’ This is simply not correct.

It is not clear why the application proposes changing the listing. Amphotericin is on the EML, appropriately listed as a complementary medicine. The applicant needs to make a case for the need to move the product to the Core List.

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

There is no basis to amend the current listing.

References