Expert peer review on application for inclusion of bedaquiline

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes

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

There is data only on Phase 1 and phase 2 clinical trials. The drug has been tried only on around 600 patients. The addition of bedaquiline to a standard 5 drug regimen resulted in sputum culture negative conversion in 48% patients compared to 9% in the placebo group at the end of 8 weeks. In a similar study conducted over 24 weeks, the proportion of patients with culture conversion were 79% in the bedaquiline group and 58% in placebo group, (p=0.008). Their follow up at 96 weeks revealed 62% patients on bedaquiline remaining culture negative compared to 44% of placebo group. This limited data shows that the drug is effective in MDR-TB when added to second line anti tubercular drugs.

c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes

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

Since only small numbers of patients have been treated with the drug, safety data cannot be commented upon. The adverse effects reported during the phase 1 and phase 2 studies range from serious events such as pancreatitis and QT prolongation to mild ADRs like dizziness. However, the studies that have been done will not pick up rare adverse events which will need much larger data sets.

c. Please provide any additional relevant information with reference

An increased risk of death was seen in the bedaquiline group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf)

3. Assessment of cost and availability
a. Have all relevant data on safety 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)

Bedaquiline has just been approved in USA. The cost is not known yet. It is not available anywhere else in the world at the moment. Cost-effectiveness has been worked out in the provided review based on hypothetical figures as there have been no large scale studies done to date.

c. Please provide any additional relevant information with reference

Nil

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

No. The product is not available in any of the LAMIC.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

Appropriate treatment of MDR-TB remains a challenge globally. A faster sputum culture conversion and fewer treatment failures resulting from the addition of bedaquiline to second-line drug regimens would significantly reduce the transmission of multidrug-resistant bacteria. However, this product will be useful only if the initial observations can be successfully proved in large clinical trials in different settings and countries.

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

As the drug has not yet been approved in any other country other than USA, it is not listed in any of the guidelines.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

Yes. The drug has to be used only in DOTS programme, in combination with other drugs.

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

It has only been approved by US FDA in December 2012. No other regulatory authorities have registered it.

7. Any other comments

As bedaquiline is not available in any country at the present time and has not been included in any guideline as yet, this proposal should not be considered.

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

There is not enough evidence of efficacy and safety to justify including this drug in the EML. This drug is registered only in USA and not in any of the other countries. It is not yet available in any of the countries. Only phase 1 and 2 clinical trials have been done which limits the efficacy and safety data since the number of patients on whom the drug has been tried are few in number. The cost of the drug is also not known.
There may be safety issues which will become evident only when larger studies are done. The US FDA website clearly gives a boxed warning on the increased deaths in one trial. Though MDR-TB is a serious concern, including a drug like bedaquiline which has the potential to become a useful agent for this condition, even before published data on efficacy and safety is available, goes against the basic guidelines of selection of essential medicines. Hence this drug should not be included in the WHO EML at this point of time.