Expert peer review on application for Bedaquiline, 100 mg tablet

**Indication:** for treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB) among adults (>18 years) as part of combination therapy.

1. **Assessment of efficacy**
   a. Have all relevant studies on efficacy been included
      - Yes   No (if no, please provide reference and information)


      Industry trials summarized, not enough information to assess risk of bias. Not published.

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

      Trial (open label) comparing to monotherapy in treatment naïve patients showed greater decreases in bactericidal activity (CFU) for comparators than bedaquiline, especially early in time course. Another trial showed favorable bactericidal activity compared to placebo.

      Third trial: In Stage 2, 160 patients with MDR-TB were randomized and assigned to receive either bedaquiline (400 mg once-daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) or placebo, in combination with a standard five-drug, second-line anti-TB regimen. The primary efficacy end point was time to culture conversion using Week 24 data. The proportion of patients with culture conversion at Week 24 was 79% in the bedaquiline group and 58% in the placebo group. Data for additional trial shown in graphic form.

   c. Please provide any additional relevant information with reference

2. **Assessment of safety**
   a. Have all relevant studies on safety been included
      - Yes   No (if no, please provide reference and information)

      Not clear –265 patients exposed

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

      Unclear - adverse event that appeared in “2% or more patients” listed – shown in table 11.1 does not appear different than placebo
c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on availability been provided
      Yes No (if no, please provide reference and information)
      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)
     Used a state-space economic model to calculate in Peruvian setting: The proportion of patients with culture conversion at Week 24 [missing = failure] was 79% in the bedaquiline group and 58% in the placebo group.
   c. Please provide any additional relevant information with reference
     Currently only one manufacturer in India
   d. Is the product available in several low and middle income countries?
     Unknown

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences)
     MDR TB is a public health problem
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
     Not yet, but under consideration for WHO TB guideline update or “emergency guidance”

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences
   The application requests inclusion within the Complementary List of 6.2.4 Antituberculosis medicines under the statement ‘Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centers adhering to WHO standards for TB control’ is requested.

6. Is the proposed product registered by a stringent regulatory authority?
   No – under review by FDA, EMA

7. Any other comments
   Application is premature

8. What is your recommendation to the committee (please provide the rationale)
   Do not add