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

April 8-12 2013

Expert peer review on application to add Clozapine

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)

At present only first generation antipsychotics (FGA) are in the EML. Clozapine is superior to FGAs but is recommended only in treatment resistant schizophrenia in view of it’s severe side effects. Metanlyses show that Clozapine has equivalent and probably superior efficacy to Risperidone in terms of number of people who left the study.

   c. Please provide any additional relevant information with reference

In a 2006 open label study\(^1\) of schizophrenia patients who had failed a trial of second generation antipsychotic (SGA), patients on clozapine had a significantly longer time to discontinuation than those on quetiapine, olanzapine or risperidone suggesting better efficacy.

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)

Clozapine can cause severe life threatening agranulocytosis and should be prescribed only in patients who can undergo regular testing of blood counts. In comparison to haloperidol and chlorpromazine, it is more likely to cause weight gain and metabolic abnormalities and less likely to cause extrapyramidal symptoms (EPS).

   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)

Clozapine is significantly more costly than FGAs. There is no published data on cost effectiveness of Clozapine.

   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)

   The need is for treatment resistant schizophrenia

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

   Yes for treatment resistant schizophrenia with careful monitoring.

   FDA, NICE 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. Weekly monitoring of blood counts for 6 weeks and then monthly till one month after discontinuation. Cannot be used in patients on other agents that potentially cause agranulocytosis and in patients with myeloproliferative disorders.

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

7. Any other comments

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

   I recommend that Clozapine not be included in the EML. I suggest that another SGA be introduced first. The regular monitoring that is required to screen for agranulocytosis may be very difficult in low to middle income countries.

REFERENCES