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

April 8-12 2013

Expert peer review on application for inclusion of clozapine (as a complementary medicine)

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

   An additional Cochrane review, comparing atypical antipsychotics, was published in the 2012 edition, but had been completed in 2000 (Tuunainen A, Wahlbeck K. Newer atypical antipsychotic medication versus clozapine for schizophrenia. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD000966. DOI: 10.1002/14651858.CD000966). The review included data from eight studies (22 papers; a total of 795 participants), of which three studies were of very short duration (4-6 weeks) and only one was of more than 12 weeks’ duration (but still considered medium duration). This review specifically sought evidence on the outcomes achieved in cases of treatment-resistant schizophrenia. In this analysis, the results for all other atypicals were grouped and compared with those for clozapine. Some risk of bias was identified for all included studies.

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

      As with the data presented in the proposal, this review failed to show any strong evidence of a difference in efficacy between clozapine and other atypical antipsychotics. The authors’ conclusions were thus: “Newer atypical drugs seemed to be broadly similar to clozapine using a clinical global index or trialists’ definitions of improvement, but this result was obtained from a relatively small number of studies. Due to the small number of studies and patients, wide confidence intervals were seen when their effectiveness as measured by symptom rating scales was compared. Social functioning was better in patients on newer atypical medication (risperidone) than in those on clozapine, but this finding is based on a single underpowered trial and has to be interpreted with caution”.

   c. Please provide any additional relevant information with reference

      The included Cochrane Review by Essali et al. (Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000059. DOI: 10.1002/14651858.CD000059.pub2) was updated in 2010, with no change to the conclusions reached in 2009.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes  No ✓
      (if no, please provide reference and information)
As above (to include the review reported as Tuunainen A, Wahlbeck K. Newer atypical antipsychotic medication versus clozapine for schizophrenia. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD000966. DOI: 10.1002/14651858.CD000966).

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

The authors’ conclusion was that: “Clozapine and newer atypical drugs showed their adverse effect profile to be dissimilar: while clozapine produced more fatigue, hypersalivation, nausea, and orthostatic dizziness, new atypical drugs, with the exception of olanzapine, produced more extrapyramidal symptoms.” This is in line with the data presented in the proposal.

c. Please provide any additional relevant information with reference

See above.

3. Assessment of cost and availability

a. Have all relevant data on cost and availability been provided
   Yes ✓ No (if no, please provide reference and information)

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)

Prices of clozapine differ widely between settings, based on the data in the MSH International Drug Price Indicator Guide. There are generic versions available.

c. Please provide any additional relevant information with reference
d. Is the product available in several low and middle income countries?

This product is available in a number of countries. However, there is increasing access to generic versions of other atypical antipsychotics, notably risperidone in several countries.

4. Assessment of public health need

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

The public health need for antipsychotic medicines is justified by the global burden of disease. Given the proportion of patients who do not respond to or cannot tolerate first-line typical antipsychotics, the need for a second-line option is supported. That such an option might be included in the complementary list is also supported.

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

Clozapine is included as one of many atypical agents that may be considered, according to:
5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

In some countries, supply of clozapine is directly linked to the provision of a full blood count determined by an accredited laboratory. Such interventions may not be legally enforceable in all countries.

6. Is the proposed product registered by a stringent regulatory authority?
   - Yes ✓  No

7. Any other comments

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

This application needs to be considered in the light of the competing application for the addition of risperidone, which is also a second-generation or atypical antipsychotic, but without the haematological adverse effect profile of clozapine. Risperidone has in the past been far more expensive than the first-generation agents, but is increasingly available in generic versions and at far more affordable prices. Although risperidone is associated with a different set of potential adverse effects, it represents a better option for addition to the WHO Model EML, in order to meet the clearly demonstrated need for an alternative to the listed first-generation antipsychotics. It is therefore recommended that the addition of clozapine not be approved.