Expert peer review on application for fluoxetine age restriction for the treatment of depression from > 8 years to >12 years

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

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

   As stated in the application "For most SSRIs, the evidence is sparse and so it is not possible to determine if there is a clinically important difference between individual SSRIs and placebo. For fluoxetine, in terms of responders and in terms of score on a depression measure, there is limited evidence suggesting a significant beneficial effect"

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)

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

   In terms of treatment acceptability and adverse effects, the evidence is sparse and inconclusive. In terms of suicide ideas/behaviour, for the group of selective serotonin reuptake inhibitors, including children and adolescents together, there is evidence of a significant increased risk (RR 1.73, 1.13 to 2.67, absolute risk difference 2.5%). For the other critical outcomes, no evidence is available.

c. Please provide any additional relevant information with reference

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

c. Please provide any additional relevant information with reference

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

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

   Currently fluoxetine is a complementary medicine for children >8 years in WHO essential list of medicines for children. It seems that moving this age to > 12 years would be a more prudent risk-benefit decision

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

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

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)**

   The application states the "Taking into consideration the lower incidence and prevalence of depression in younger children, the evidence reviews on the effectiveness or adverse effects of the medicine for younger age group, the realities of child mental health services in many low resource settings which might favour over-prescription, and the overall risk-benefit aspects; we suggest to increase of the age limit from >8 years to >12 years".

   **I strongly recommend to increase the age limit as requested (only above 12 years of age) given the magnitude of expected benefits and the lack of evidence for many beneficial outcomes.** The EML could also reconsider the overall benefit risk profile of fluoxetine also for the remaining 12-18 yrs population for which the evidence of benefit is of dubious clinical relevance and also evaluate the overall risk benefit profile taking into account the negative data for all other antidepressants.