Expert peer review on application for updating 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
   
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      There is only modest evidence of the efficacy of fluoxetine in childhood depression (defining “childhood” as <12 years) and the quality of evidence is low. Several reviews have pointed out the relative lack of evidence on efficacy of antidepressants available for this age group. Of the existing SSRIs, fluoxetine alone has evidence of efficacy in this age group. However, the magnitude of this effect, the risk-benefit ratio, the risk of a rare but fatal adverse event (suicide), suicidal ideation and concerns over misdiagnosis and over-prescription still remain.
   
   c. Please provide any additional relevant information with reference
      Expert opinion still supports the use of fluoxetine in children if the diagnosis of depression is confident (Andrade C, Bhakta SG, Singh NM. Controversy revisited: Selective serotonin reuptake inhibitors in paediatric depression. World J Biol Psychiatry. 2006;7(4):251-60.) However, since the diagnosis of depression in children is not easy, this becomes a factor that must be taken into account, considering the differences in quality of mental healthcare available in different parts of the world.

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

      One study on the risk of aggressive behaviour with fluoxetine in this age group has not been included. (Tauscher-Wisniewski S, Nilsson M, Caldwell C, Plewes J, Allen AJ. Meta-Analysis of Aggression and/or Hostility-Related Events in Children and Adolescents Treated with Fluoxetine Compared with Placebo. Journal of Child and Adolescent Psychopharmacology. October 2007, 17(5): 713-718. doi:10.1089/cap.2006.0138.) The study concludes that there is no significant difference between placebo and fluoxetine treatment and failed to support an association between fluoxetine treatment and increased risk of aggression and/or hostility-related events in children and adolescents compared with placebo.
   
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
There is a significantly elevated risk of suicidal thoughts and possibly of suicidal behaviour, especially in the initial four weeks of treatment, in patients <25 years of age who receive fluoxetine. However, there is no clear evidence that this risk is higher in those <12 years.

c. Please provide any additional relevant information with reference

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)

   There are no systematic studies on the cost-effectiveness of fluoxetine therapy in depressed children. However, on practical grounds, fluoxetine is less costly than psychotherapy in many settings. The efficacy of psychotherapy in young children is also debatable. In LAMIC psychotherapy is provided by general psychiatrists or pediatricians or other healthcare workers. Hence even if psychotherapy is less costly in LAMIC, the quality may be questionable.

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)

   Childhood depression may affect up to 2-3% of pre-pubertal children. It can lead to significant academic and interpersonal difficulties. Later in life, adults with childhood onset depression are more likely to develop other (co-morbid) psychiatric disorders, as well as to attempt suicide. Studies have shown that the overall prevalence of depression in children under 13 years old was 2.8% (SE=0.5%)

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

   Yes, with precautions. Both the UK (NICE) and US (AACAP) guidelines recommend using the drug with caution, and with frequent supervision, in younger children, preferably in conjunction with psychotherapy.

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

   If yes, please provide details in 1-2 sentences

   Because of the risk of suicide, other behavioural side-effects, and possible treatment-emergent mania, this drug should be used under the supervision of a psychiatrist with sufficient exposure to child and adolescent psychiatry.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes
7. Any other comments

The provided review is an excellent compilation of evidence with respect to use of fluoxetine in children. Evidence for the efficacy of both pharmacotherapy and psychotherapy in young children is limited (Kapornai K, Vetró A. Depression in children. Curr Opin Psychiatry. 2008 Jan;21(1):1-7. doi: 10.1097/YCO.0b013e3282f25b01.). A more recent systematic review clearly states that there is no robust evidence of antidepressant efficacy in children aged 10 or below (Gentile S. Antidepressant use in children and adolescents diagnosed with major depressive disorder: what can we learn from published data? Rev Recent Clin Trials. 2010 Jan;5(1):63-75.) In a meta-analysis of drug trials in juvenile depression, the number needed to treat was high in children (NNT=21), but lower and more clinically acceptable in adolescents (NNT=8). The most recent Cochrane review suggests that antidepressants have only modest efficacy in young children (Hetrick et al., 2012 ref No 22), and also found a significantly elevated risk of suicidal events (risk ratio 1.58 for antidepressants vs placebo).

A review of antidepressant trials suggests that placebo response rates are higher in younger children than in adolescents, suggesting that non-specific factors may contribute more to their apparent improvement (Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. Am J Psychiatry. 2009 Jan;166(1):42-9) while another study found that placebo response rates in fluoxetine trials were actually lower in children than in adolescents. (Mayes TL, Tao R, Rintelmann JW, Carmody T, Hughes CW, Kennard BD, Stewart SM, Emslie GJ. Do children and adolescents have differential response rates in placebo-controlled trials of fluoxetine? CNS Spectr. 2007 Feb;12(2):147-54.)

It has been suggested on ethical grounds that given the uncertain benefits vs. the known risks of antidepressant treatment in children, it is better to err on the side of caution (Shearer MC, Bermingham SL. The ethics of paediatric anti-depressant use: erring on the side of caution. J Med Ethics. 2008 Oct;34(10):710-4).

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

On precautionary grounds, the use of fluoxetine in pre-pubertal children cannot be accepted at the present time. The authors’ recommendation of a cut-off of >12 years is reasonable, given the presented evidence and should be implemented, though risks remain even in older children and adolescents.