Reviewer No.1 checklist for application for addition: Fluoxetine 20mg tablets [As representative of the Selective-Serotonin Reuptake Inhibitors’ (SSRIs) Class]

(1) Have all important studies that you are aware of been included?
   Yes √ No

Additional critical reviews and meta-analysis on the efficacy and safety of SSRIs for the treatment of depression include:


(2) Is there adequate evidence of efficacy for the proposed use?
   Yes √ No

There is robust evidence suggesting that SSRIs are as effective as tricyclic antidepressants for the treatment of depression. Most treatment guidelines recommend a generic SSRI in the first line pharmacological treatment of moderate to severe depression:

- The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Canadian Psychiatric Association (CPA) (2001)
- The American Psychiatric Association (APA) Practice Guidelines consider SSRIs among other medications (desipramine, nortriptyline, bupropion and vanflaxine), optimal for most patients (2005).

Fluoxetine was introduced as the first medication in the group of SSRIs during the 1980s, and the first one to become available in generic form.
(3) Is there evidence of efficacy in diverse settings and/or populations?

Yes √ No

**Elderly:** The prevalence of depression among people aged over 65 is reported to be between 15% and 40% among different settings (Macdonald AJD. ABC of mental health: Mental health in old age: Clinical Review. BMJ 1997;315:417). The highest rates of depression in the elderly are found in patients with strokes, coronary artery disease cancer, Parkinson’s disease, and Alzheimer’s disease. The recurrence rate is also extremely high at 40 percent (Birrer RB, Vemuri SP. Depression in later life: a diagnostic and therapeutic challenge. Am Fam Phys 2004;69:2375-82).

Elderly patients are more susceptible to anticholinergic effects and have a greater liability to particular side effects of tricyclic antidepressants such as postural hypotension and cognitive impairment. Some authors recommend avoiding the use of amitriptyline in this patient population, (Spigset O, Martensson B. Drug treatment of depression: Clinical Review. BMJ 1999: 318:1188-1191).

**Child and Adolescent:** Depression is a common but under recognised problem in young people. Its estimated prevalence is 1.9% in primary school children, rising to 4.7% in adolescents. Depression may be present in more than half of child and adolescent psychiatric inpatients. Important consequences of depression in this age group include social dysfunction, academic underachievement, and suicidal behaviour. Consequently, adequate detection and treatment of depressed adolescents is an important strategy for curbing the rising rate of suicide in youth.

Several studies indicate the use of fluoxetine for depression in children and adolescents:


- Results from a large study conducted by the National Institute of Mental Health in the USA, indicate that a combination of fluoxetine and cognitive behaviour therapy is the most effective treatment for major depressive disorder in adolescents. (Elkin I, Gibbons ID, Shea T, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health. Treatment of Depression Collaborative Research Program. J Consult Clin Psychol. 1995;63:841-847.)
Are there adverse effects of concern?

Yes √ No

Reported side effects of fluoxetine include headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, dizziness or light-headedness, nausea, dry mouth, diarrhoea, anorexia, and excessive sweating.

Some studies have reported that SSRIs possibly increase the risk of suicide and suicidal ideation, particularly in adolescents. Worldwide regulatory authorities have issued warnings about the risk of self-harm and suicidal ideation in children, adolescents and adults taking antidepressants [Food and Drug Administration. Antidepressant use in children, adolescents and adults. Available at http://www.fda.gov/cder/drug/antidepressants/default.htm (Accessed January 2007)]. However, forensic analysis, and drug discontinuation studies seem to indicate that in fact, the prescription of antidepressants, including SSRIs, reduces suicidal behaviour and completed suicide attempts overall and in adolescents. In recent case-controlled forensic analysis of nearly 15,000 suicides, the presence of different antidepressants was determined to be lower than for other antidepressants with a slight increase of suicidal ideation in the initial stages of treatment [Isacsson G, Holmogren P, Ahlner J, et al. Forensic database study suggest selective serotonin reuptake inhibitors do not increase the risk of suicide in people taking antidepressants. Acta Psychiatr Scand; 111:286-90 (2005)] and [Anderson IM. Meta-analytical studies on new antidepressants, British Medical Bulletin 57:161-178 (2001)].

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

Yes √ No

Is this product needed to meet the majority health needs of the population?

Yes √ No

Depression is the fourth leading cause of disease burden, accounting for 4.4% of total DALYs in the year 2000, and it causes the largest amount of non-fatal burden, accounting for almost 12% of all total years lived with disability worldwide. It represents a major public health problem that affects patients and society around the world (Üstün TB, Ayuso-Mateos JL, Chatterji S, et al. Global burden of depressive disorders in the year 2000 The British Journal of Psychiatry (2004) 184: 386-392).

Is the proposed dosage form registered by a stringent regulatory authority?

Yes √ No

- Fluoxetine is the only antidepressant approved by the FDA in the USA for the treatment of major depressive disorder in patients 8 years or older.
- The European Medicines Agency approved the use of fluoxetine for children aged 8 years or more and teenagers who have moderate to severe depression in

(8) **What action do you propose for the Committee to take?**

Include fluoxetine 20mg tablets in the Model List as a representative of the SSRI group of medications for the treatment of depression.

(9) **Additional comment, if any.**

Currently, the WHO Model List has only amitriptyline listed for the treatment of depression. Several important reasons justify the addition of fluoxetine to the Model List:

First, according to reports based on CR and meta-analysis, total discontinuation rate is reported 10% lower with SSRIs than with tricyclic antidepressants and the drop out rate due to side effects is 25% lower. Studies have demonstrated that patients tend to tolerate better SSRIs and report less AEs than with tricyclic antidepressants. (Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. BMJ 1995:310:1433-1438).

Second, SSRIs have a more benign cardiovascular profile and are the preferred initial agents for treatment of depression in individuals with cardiovascular disease. [Institute for Clinical Systems Improvement (ICSI). Major depression in adults in primary care: Clinical Guidelines. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 May. 81 p. [201 references].


Fluoxetine should be indicated as the first line of treatment when:

- Suicide risk due to overdose is present
- Cardiac conditions (especially conduction abnormalities) are present
- Other medical conditions are present which could be exacerbated by tricyclic side-effects (e.g., orthostatic hypotension, benign prostatic hyperplasia (BPH), glaucoma, seizures, chronic constipation)
- Patient is less than 18 years old and has been diagnosed with moderate to severe depression
The addition of SSRIs will give a strong message from WHO regarding the importance of keeping patients with depression under treatment by listing an alternative medication for patients who have low compliance, drop out of treatment due to the adverse effects of the tricyclic antidepressants or for whom tricyclic antidepressants are not safe or effective.