

I.4	Fluoxetine – anxiety disorder – EML
Draft recommendation	<input checked="" type="checkbox"/> Recommended <input type="checkbox"/> Not recommended <p>Justification:</p> <p>Anxiety disorders can be treated by SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and benzodiazepines (BZDs). SSRIs are recommended as the first-line pharmacological treatment, as they are more effective in reducing anxiety symptoms than placebo and have a safer profile than the above-mentioned therapeutic classes, including in case of acute intoxication.</p> <p>Currently, the Section 24.3 “Medicines for anxiety disorders” includes only diazepam and no antidepressants are listed in this section. Fluoxetine may be included in the EML in Section 24.3 “Medicines for anxiety disorders” for generalized anxiety disorder, panic disorder, and social anxiety disorder” with a square box symbol. This square box symbol is currently restricted to citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline which could be substituted to include fluoxetine as a therapeutic alternative.</p> <p>SSRIs are essential medicines in low- and middle-income countries (LMICs), due to their efficacy, safety profile, worldwide availability and affordability, and ease of administration (one daily oral intake). These medicines are worldwide available as generics and included in most national pharmacopoeias.</p>
<p>Does the proposed medicine address a relevant public health need?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <p>Comments:</p> <p>Anxiety disorders are receiving more and more attention, due to their high incidence, early age of onset, and tendency to relapse for a long time and for their disabling nature.³ anxiety disorders are major drivers of the global burden of disease, as measured in prevalence, disability-adjusted life-years, and years lived with disability. In the last 20 years both depressive and anxiety disorders have consistently been among the top ten leading causes of all years lived with disability (YLD) worldwide (WHO Report). The COVID-19 pandemic has had a large and uneven impact on global mental health, rise in anxiety disorders especially in countries with high COVID-19 infection rates and a consequence of measures major reductions in the movement of people (lockdowns and school closures). Women were affected more frequently than men, and younger people were more affected than older age groups.</p>
<p>Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <p>Comments:</p> <p>Metanalysis and systematic review of the randomized controlled trials (RCTs), have shown that fluoxetine is effective in reducing symptoms of panic disorder, generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder.</p>

<p>Does adequate evidence exist for the safety/harms associated with the proposed medicine?</p> <p>(this may be evidence included in the application, and/or additional evidence identified during the review process)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Fluoxetine is a safe medication. Common adverse effects include nausea, diarrhea, dry mouth, headache, and insomnia. These side effects are generally mild and temporary and may improve over time as the body adjusts to the medication.</p> <p>Fluoxetine may also increase the risk of suicidal thoughts and behaviors in children, adolescents, and young adults with depression or other psychiatric disorders. Therefore, the FDA requires a black box warning on fluoxetine and other antidepressant medications regarding this risk. Patients' needs to be monitored closely for any changes in mood or behavior while taking fluoxetine, particularly during the first few weeks of treatment or after a change in dose.</p> <p>Fluoxetine may interact with other medications and supplements, and it should be used with caution in patients with liver or kidney disease, diabetes, or a history of seizures.</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Fluoxetine is a well-tolerated medicine but has a potential for an increased risk of suicidal thoughts and behaviors, particularly in children, adolescents, and young adults. Fluoxetine also increases the risk of bleeding, particularly when used in combination with other medications that affect blood clotting, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants. Fluoxetine may also cause hyponatremia, can cause symptoms such as headache, nausea, vomiting, confusion, and seizures. Other adverse effects of fluoxetine may include sexual dysfunction, weight gain, and sleep disturbances.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicines?</p> <p>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Fluoxetine has a potential for an increased risk of suicidal thoughts and behaviors, particularly in children, adolescents, and young adults. Patients need to be closely monitored for any changes in mood or behavior, particularly during the first few weeks of treatment or after a change in dose.</p>

<p>Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>In general, fluoxetine is available as a generic medication, which is typically less expensive than brand-name versions. Fluoxetine has been found to be more cost-effective than placebo and other antidepressant medications for treating social anxiety disorders and panic disorder. However, the cost-effectiveness of fluoxetine may vary depending on factors such as the severity of the disorder and the patient's response to treatment. Access to fluoxetine may be a concern in some settings. In some countries, fluoxetine may be less widely available or may be more expensive than in others. In addition, some patients may have difficulty accessing healthcare services where they can receive a prescription for fluoxetine.</p>
<p>Are there any issues regarding the registration of the medicine by national regulatory authorities?</p> <p>(e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Fluoxetine is approved by the US FDA and the EMA for the treatment of several anxiety disorders, including panic disorder, social anxiety disorder, and obsessive-compulsive disorder. It has not been approved for the treatment of generalized anxiety disorder. Use in generalized anxiety disorder, fluoxetine use is mainly off-label though various guidelines (NICE, British Association of Psychopharmacology (BAP), The Royal Australian and New Zealand College of Psychiatrists (RANZCP) recommend SSRIs as the first-line medications for panic disorder, social anxiety disorder and generalized anxiety disorder.</p>
<p>Is the proposed medicine recommended for use in a current WHO guideline?</p> <p>(refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The Guidelines Development Group of WHO Mental Health Gap Action Programme (mhGAP) has proposed revision recommending that SSRIs should be considered for adults with panic disorder and generalized anxiety disorder.</p>