D.6	Fluoxetine – depression – EMLc deletion
Draft recommendation	☐ Recommended ☒ Not recommended Justification: deletion not recommended Depression in children is not rare, although it may be underdiagnosed and undertreated, having significant impact on a child's quality of life, social and academic functioning, and overall health and well-being. According to the World Health Organization (WHO), an estimated 3.9% of children aged 5-19 years' experience depressive disorders. The prevalence of depression in children increases with age, with the highest rates reported among adolescents. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant commonly used in children and adolescents for the treatment of major depressive disorder, obsessive-compulsive disorder, and other psychiatric conditions. The medication has been shown to be effective for these indications. While more research is needed to fully understand the best approaches for treating depression in children, The potential increased risk of suicidal thoughts and behaviors, particularly in the early stages of treatment can be mitigated by close monitoring by a healthcare provider. Untreated depression can have serious consequences on their emotional, social, and physical development such as social isolation, loneliness, academic problems, substance abuse (may turn to drugs or alcohol to cope with their emotions), self-harm. In the most severe cases, untreated depression can lead to suicidal thoughts or attempts. Despite the scarcity of high-quality evidence, fluoxetine (alone or in combination with cognitive behavioral therapy) seems to be the best choice for the acute treatment of moderate-to-severe depressive disorder in children and adolescents. While WHO Mental Health Gap (mhGAP) guidelines do not make any specific recommendation for children and do not recommend pharmacological treatment with fluoxetine for children younger than 12 years but in LMICs, with limited access to mental health services, and shortage of mental health professionals for non-pharmacological management, pharmacological management (fluoxetine and escitalopram) remains the mainstay of treatment. Currently, fluoxetine is the only antidepressant included in the EMLc. Its deletion would imply the absence in EMLc of pharmacological treatment for children with depression. Various guidelines also recommend its use for depression and anxiety disorders in children and adolescents.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Depression is a significant problem in children and adolescents, with a considerable impact on their well-being and development. According to the World Health Organization (WHO), depression is one of the leading causes of disability and disease burden in young people aged 10-24 years old globally. The prevalence of depression in children and adolescents varies by country and population, but estimates suggest that around 3.9% of children and adolescents globally experience depression. In the United States, approximately 2% of children aged 6-12 years old and 5-8% of adolescents aged 13-18 years old experience major depressive disorder. Depression in children may present differently than in adults, and can manifest as irritability, unexplained physical symptoms, academic difficulties, and social withdrawal, among other symptoms. Depression can have a significant impact on a child's functioning, including academic performance, social relationships, and overall quality of life. Untreated depression can also lead to increased risk of suicide and other negative outcomes.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: There is some evidence specific to the treatment of depression in children, although much of the available research focuses on adolescents. There are small number of studies that specifically include children as a separate population from adolescents. One reason for the lack of research specifically focused on children is that depression can be difficult to diagnose in young children, who may not be able to articulate their feelings and symptoms as clearly as older children or adolescents. Additionally, treatment approaches for depression in children may differ from those used for adolescents or adults. Despite these challenges, there have been some clinical trials and observational studies that have included children in their samples, with a focus on evaluating the safety and efficacy of various treatment approaches for depression in this population. For example, the Treatment for Adolescents with Depression Study (TADS) included children aged 12-14 in its sample, while the Treatment of Resistant Depression in Adolescents (TORDIA) study included participants aged 12-18, with a separate analysis of the data specifically for the younger participants. Fluoxetine is considered as a treatment option for depression in children aged 8-12 years old, but the decision to use this medication should be made on a case-by-case basis. It has been approved by the US FDA for the treatment of major depressive disorder in children aged 8-18 years old.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: Fluoxetine has been studied in clinical trials involving children and adolescents with depression, and its safety profile has been established. While fluoxetine is generally considered safe and effective for the treatment of depression in children, it is not without risks. Fluoxetine has been associated with an increased risk of suicidal ideation and behavior, as well as behavioral changes, serotonin syndrome, abnormal bleeding, growth and development issues, and sexual dysfunction. These risks are generally low, but they should be carefully monitored in children taking fluoxetine. Untreated depression can have serious consequences on their emotional, social, and physical development such as social isolation, loneliness, academic problems, substance abuse (may turn to drugs or alcohol to cope with their emotions), self-harm: In the most severe cases, untreated depression can lead to suicidal thoughts or attempts.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Children treated with fluoxetine need close monitoring for adverse effects, including suicidal ideation, behavioral changes, and worsening of depression or anxiety. Monitoring is required for potential drug interactions and adverse effects such as weight gain, insomnia, and gastrointestinal symptoms.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Fluoxetine should be used in the treatment of major depressive disorder in children aged 8 years and above only after a thorough psychiatric evaluation to establish a diagnosis. The starting dose of fluoxetine in children should be low and individualized based on the patient's age, weight, and clinical response, with gradual increase in dose as needed. Children need close monitoring for adverse effects and clinical response. The duration of treatment with fluoxetine should be based on the patient's clinical response and should be continued for a sufficient period, usually several months, to ensure a sustained response and to minimize the risk of relapse. Fluoxetine should be discontinued gradually, rather than abruptly, to avoid withdrawal symptoms such as dizziness, nausea, and headache.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Some data are available on the cost-effectiveness of antidepressant medications for children. Data on adults is not generalizable to children. There is ongoing debate about the cost-effectiveness of fluoxetine for the treatment of depression in children and adolescents and there are issues regarding affordability, and access to fluoxetine for children and the potential need for ongoing treatment can be a barrier for some families and healthcare systems particularly in low- and middle-income countries. In low- and middle-income countries, there may be limited availability of trained mental health professionals who can diagnose and treat depression in children, which can further limit access to effective treatment. Also, data for cost-effectiveness is not available as pharmacological treatment is not recommended as first line treatment with fluoxetine for children younger than 12 years. In some countries, fluoxetine may be relatively expensive, making it less accessible to those who cannot afford it or who do not have access to health insurance.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Fluoxetine is approved by the U.S. FDA for the treatment of major depressive disorder in children and adolescents aged 8-18 years old. Fluoxetine is also approved for the treatment of obsessive-compulsive disorder, bulimia nervosa, and panic disorder in children and adolescents. In other countries, fluoxetine may have different regulatory statuses for use in children. In the European Union, for example, fluoxetine is approved for the treatment of major depressive episodes in children and adolescents aged 8-18 years old, as well as for the treatment of obsessive-compulsive disorder in children aged 7 years and above. The EMA did not recommend the use of fluoxetine in children and adolescents (under the age of 18) as “safety and efficacy have not been established”. Central Drugs Standard Control Organization (India) and South African Health Products Regulatory Authority: No regulatory information is given for fluoxetine in children. Of the other SSRIs approved by the US FDA for adults, none is approved for children. Escitalopram is approved for adolescents (13–17-year-olds). All the other SSRIs (citalopram, fluvoxamine, sertraline, paroxetine) are approved only for adults.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: WHO Mental Health Gap (mhGAP) guidelines 2019 No specific recommendation for children. Recommendations address a mixed children-adolescent population. Strong recommendations against the use of pharmacological treatment can be found in the "child and adolescent mental and behavioural disorders" chapter, section "Emotional Disorder or Depression": **DO NOT** consider pharmacological treatment as first line treatment. However, fluoxetine is recommended for the treatment of depression in children and adolescents by some clinical guidelines and protocols, including the American Academy of Child and Adolescent Psychiatry (AACAP) and the National Institute for Health and Care Excellence (NICE) in the UK recommend fluoxetine as first-line medication for depression and anxiety disorders in children and adolescents and that antidepressant medication alone could be considered, particularly if the presentation is severe and the patient is unable to engage in talking therapy, if psychological interventions are not available, or if this is the patient's and family's preference. Fluoxetine is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks (NICE). The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved fluoxetine for children and adolescents aged 8 years and above. The EMA states that the indication is moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions, antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy. It has also been shown to be effective for the treatment of other psychiatric conditions, such as obsessive-compulsive disorder, panic disorder, and bulimia nervosa, in pediatric populations.