D.3	Chlorpromazine and haloperidol – psychotic disorders – EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Haloperidol and chlorpromazine have been included on the EMLc since the first list was published in 2007. In 2013 a request for deletion of haloperidol and chlorpromazine from the WHO EMLc was submitted by the WHO Department of Mental Health and Substance Abuse. The WHO Expert Committee recognized that the indications for using chlorpromazine and haloperidol are very rare in children, and that adverse events from these medicines may be more frequent in children than in adults. However, the Committee recognized the importance of ensuring that treatment is available for severe psychiatric disorders in children and noted that the application did not fully review all treatment options. The Expert Committee therefore requested a specific review of the evidence for the benefits and risks of each medicine in the paediatric population and decided to make no changes to the list until such reviews had been considered. The applicant again proposed the deletion of the two first-generation antipsychotics (FGAs) (a) haloperidol and (b) chlorpromazine both in their oral and injectable form from the complementary list of the WHO Model List of Essential Medicines for Children, section 24.1 “Medicines for mental and behavioural disorders, Medicines used in psychotic disorders”. The identified evidence for haloperidol (4 RCTs, 144 children) and chlorpromazine (1 RCT, 60 children) is inconclusive and insufficient to support ongoing inclusion of these medicines in the EMLc for the treatment of psychoses in children. While there is basically no evidence on the safety of oral chlorpromazine in the children population, with respect to injectable formulations. NICE Guidelines recommend against rapid tranquillization using chlorpromazine, highlighting a number of side effects including acting as a local irritant if given intramuscularly. FDA did not label haloperidol muscular injections for children, as “controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted”. Based on reviewer’s clinical experience and consultation with colleagues who are child psychiatrists. There are still quite a few child patients with psychotic symptoms that need to be dealt with antipsychotics (usually off-label use). The SGAs are first choice for the treatment, we haven’t used haloperidol or chlorpromazine for child patients with psychotic symptoms for at least 20 years.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Childhood-onset schizophrenia – onset of schizophrenia before 13 years of age(18) - is extremely rare. The prevalence is estimated to be 100 times less than the adult form of the disorder.

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: Since these drugs were introduced in the 1950s and 1960s, early studies on the efficacy of children with psychotic were rare or studies were poor qualified. And pharmaceutical companies have no interest to support studies on this area. So, the data are limited. To date, the use of antipsychotics as a class in children with psychotic symptoms is not supported by enough evidence to inform clinical practice on a safe and rational prescription. According to the GRADE criteria, the applicants evaluated as "very low" the certainty in the body of evidence from randomized-controlled trials (RCTs) assessing the efficacy and acceptability of haloperidol and chlorpromazine in children with psychotic symptoms. This means that there is very little confidence in the effect estimate. To complicate matters even more, many psychotropics prescribed to children are unlicensed or off-label. The dramatic rise in prescriptions over the last twenty years has raised concern about the potential for harm. During the last decades FGAs (such as haloperidol and chlorpromazine) were less and less prescribed because they were considered risky, poorly tolerated. As a consequence, for some years a trend favoured second generation antipsychotic (SGA) prescriptions in children. The WHO mhGAP guideline do not recognize the use of antipsychotics as a viable option for the treatment of any mental health condition in children.
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: Common side effects of Haloperidol, Chlorpromazine include extrapyramidal symptoms, tardive dyskinesia, akathisia, insomnia, anxiety, drowsiness, lethargy, weight changes, anticholinergic effects (sedation, blurred vision, constipation, and dry mouth), gynecomastia, breast tenderness, galactorrhea, menstrual irregularities, injection site reaction (depot), elevated prolactin levels, dizziness and hypotension. Serious side effects include neuroleptic malignant syndrome, tardive dyskinesia, pneumonia, arrhythmia, hypotension, hypertension, seizures, jaundice, hyperpyrexia, heat stroke, dystonia. As for the absence of evidence on long-term efficacy outcomes, the long-term effects of most antipsychotic medications on children's metabolism, neurologic function and other systems are basically unknown.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Children are more vulnerable than adults to a wide range of antipsychotic side effects: sedation, acute extrapyramidal side effects (EPS), withdrawal dyskinesia, hyperprolactinemia, weight gain with related metabolic abnormalities; the long-term impacts in this age group are unclear.

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:
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: For both medicines patents have expired, thus haloperidol and chlorpromazine are available as generics, most of the time at low purchase costs. In general, evidence on the cost-effectiveness of antipsychotics in real-world settings are heterogeneous in terms of population and setting analysed, as well as methodology employed. No cost-effectiveness analyses are available for antipsychotics in children with psychosis.
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:
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: