### Expert Committee recommendation

1. **Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children.**

   The Expert Committee recommended the deletion of chlorpromazine and haloperidol (all dosage forms) from the complementary list of the EMLc. The Committee noted that schizophrenia and other chronic psychotic disorders were rare in children younger than 12 years. The Committee agreed that the available evidence for these medicines in the treatment of psychoses in children was inconclusive and insufficient to support their ongoing inclusion on the EMLc.

2. **Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders.**

   The Expert Committee recalled the request made by the 2021 Committee for therapeutic alternatives to be reviewed for the square box listings for chlorpromazine, fluphenazine and haloperidol for treatment of schizophrenia and related psychotic disorders. The Expert Committee accepted the rationale applied by the WHO Department of Mental Health and Substance Use in identifying suitable therapeutic alternatives and made the following recommendations.

   - For immediate-acting first-generation antipsychotics, chlorpromazine (ATC codes: N05AA01) should be included as a therapeutic alternative to oral haloperidol. This recommendation, coupled with the recommendation to remove chlorpromazine injection, effectively removes the independent listing for chlorpromazine from the EML. For long-acting first-generation antipsychotics, haloperidol decanoate and zuclopenthixol decanoate should be included as therapeutic alternatives to fluphenazine.
1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. Chlorpromazine and haloperidol have been included in the EMLc for treatment of psychotic disorders in children since the first list was published in 2007. In 2013, a request for deletion of these medicines was made by the WHO Department of Mental Health and Substance Use. The Expert Committee recognized that the indications for use for chlorpromazine and haloperidol were 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 was available for severe psychiatric disorders in children and noted that the application did not fully review all treatment options. The Committee therefore requested a 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 (1).

2. Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders. Chlorpromazine, fluphenazine and haloperidol have all been included on the EML for use in the treatment of schizophrenia and related psychotic disorders since the first EML was published in 1977. At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for chlorpromazine, fluphenazine and haloperidol be reviewed and updated in 2023 (1). Thus, the EML Secretariat invited the WHO Department of Mental Health and Substance Use to submit an application reviewing the therapeutic alternatives for these medicines. In a separate application to the 2023 Expert Committee meeting, the WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation at the University of Verona, Italy, proposed the deletion of chlorpromazine intramuscular injection from the EML.
Benefits

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. The application presented the results of a comprehensive literature search for systematic reviews on the efficacy, acceptability and tolerability of antipsychotic medicines in children with schizophrenia and related psychoses. No systematic reviews were found on the efficacy of antipsychotics specifically focused on children aged 12 years or younger. Existing reviews included a mixed population of children and adolescents, largely composed of individuals between 14 and 18 years of age. Eleven systematic reviews were included (15–25), from which data from five randomized controlled trials (four for haloperidol and one for chlorpromazine) were extracted and reanalysed using standard Cochrane methodology. Data from a further three randomized controlled trials involving second-generation antipsychotics were also extracted and reanalysed (26–28). Of note, the data reviewed accounted only for oral administration of haloperidol, chlorpromazine or other antipsychotics; no evidence from randomized controlled trials was available on the efficacy of these compounds administered by intramuscular injection. The findings from trials of chlorpromazine and haloperidol are described below. For second-generation antipsychotics, as no trials have been conducted versus placebo, no information is available on the potentially beneficial role of these medications in children. Chlorpromazine A single randomized controlled trial (60 participants) evaluated the efficacy of chlorpromazine in comparison with risperidone in children and adolescents aged 7 to 16 years with a diagnosis of childhood-onset schizophrenia (29). Psychotic symptomatology at 8 weeks was evaluated using the Brief Psychiatric Rating Scale. Results showed a trend favouring risperidone over chlorpromazine (mean difference (MD) 1.80, 95% confidence interval (CI) –1.14 to 4.74). The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) certainty of evidence was judged to be very low. Haloperidol A single placebo-controlled randomized controlled trial of haloperidol in children with schizophrenia (12 participants) was not included in the meta-analysis because it had a crossover design and the results before crossing over were not available (30). Two double-blind randomized controlled trials (90 participants) compared haloperidol with fluphenazine in children with schizophrenia (31,32). Pooling the two studies for the outcome “showing moderate or marked improvement” at study endpoint showed a non-significant trend favouring fluphenazine (risk ratio (RR) 0.91, 95% CI 0.72 to 1.14). One double-blind randomized controlled trial (42 participants) compared haloperidol with risperidone in children with childhood-onset schizophrenia (33). For the outcome of psychotic symptomatology at 6 weeks as measured by the Brief Psychiatric Rating Scale, no significant difference was seen between treatments (MD 1.39, 95% CI –0.93 to 3.71).

2. Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders. The application stated that according to the most recent and high-quality meta-analysis evidence on both acute and maintenance treatment of schizophrenia spectrum disorders, differences exist between first-generation antipsychotics in terms of efficacy, tolerability and certainty of evidence. The applicants examined two recent meta-analyses: a 2019 systematic review and network meta-analysis (402 randomized controlled trials, 53 463 participants) which evaluated the comparative efficacy and tolerability of 32 oral antipsychotics for acute treatment of adults with schizophrenia (6); and a 2022 systematic review and meta-analysis (537 randomized controlled trials, 76 382 participants) which investigated the response of subgroups of patients with schizophrenia to different antipsychotic medicines (7). The evidence for first-generation antipsychotics was reviewed according to the following criteria. • Demonstration of better efficacy in comparison with placebo for acute and/or maintenance treatment, considering the effect size as clinically meaningful when the confidence interval included a standardized mean difference of ≥ 0.3 for continuous outcomes, or a risk ratio of ≥ 0.6 for dichotomous outcomes. • A moderate to high certainty of evidence according to grading of recommendations, assessment, development, and evaluations (GRADE)/confidence in network meta-analysis (CINeMA) approach for acute or maintenance treatment, or both. The first-generation antipsychotics identified as meeting the above criteria were oral chlorpromazine, immediate-acting haloperidol, long-acting haloperidol decanoate, fluphenazine enantate/decanoate and zuclopenthixol decanoate. When compared head-to-head with the first-generation antipsychotics already listed in the EML, no statistically significant differences were found.

Harms

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. Chlorpromazine From the randomized controlled trial of chlorpromazine versus risperidone, there was very low-certainty evidence of no difference between treatment arms in extrapyramidal symptoms (RR 2.0, 95% CI 0.2 to 20.9), drowsiness (RR 11.0, 95% CI 0.64 to 190.53) or anticholinergic effects (RR 2.0, 95% CI 0.40 to 10.11). No data were available for the outcomes of drop-outs for any reason or drop-outs due to adverse events (29). Haloperidol From the randomized controlled trials involving haloperidol (31–
there was very low-certainty evidence of no differences between haloperidol and other antipsychotics overall for any side-effects (RR 1.39, 95% CI 0.61 to 3.15; two randomized controlled trials, 72 participants). In one study (42 participants), there was very low-certainty evidence that haloperidol caused fewer side-effects than risperidone (RR 2.05, 95% CI 1.32 to 3.19). There was very low-certainty evidence of a trend favouring haloperidol over other antipsychotics overall for extrapyramidal symptoms (RR 1.82, 95% CI 0.33 to 10.06; three randomized controlled trials, 132 participants). There was very low-certainty evidence that haloperidol caused significantly more extrapyramidal side-effects than risperidone (RR 8.60, 95% CI 2.67 to 27.68; one randomized controlled trial, 42 participants). For weight gain, there was very low-certainty evidence of no difference between haloperidol and fluphenazine (RR 1.17, 95% CI 0.88 to 1.55; one randomized controlled trial, 30 participants). There was very low-certainty evidence that haloperidol caused significantly more drowsiness than risperidone (RR 6.50, 95% CI 1.67 to 25.33; one randomized controlled trial, 42 participants), and of no difference between treatment arms for anticholinergic side-effects (RR 7.00, 95% CI 0.38 to 127.69; one randomized controlled trial, 42 participants) (33). First-generation antipsychotics are associated with extrapyramidal side-effects (dystonia, tardive dyskinesia and parkinsonian symptoms), hyperprolactinaemia and neuroleptic malignant syndrome. Evidence indicates that side-effects may be more severe in children than in adults (34–36). No safety data are available in children exposed to long-term use of antipsychotics.

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. No cost–effectiveness analyses are available for antipsychotics in children with psychosis. Chlorpromazine and haloperidol are available as generics, mostly at low purchase prices. ========= 2. Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders. Different side-effect profiles of the different first-generation antipsychotics were observed, although tolerability outcomes were rarely reported and were likely imprecise. In general, chlorpromazine had a higher risk of weight gain and anticholinergic effects compared with haloperidol, however haloperidol was associated with higher risks of extrapyramidal symptoms, akathisia and hyperprolactinaemia than chlorpromazine.

2. Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders.

The medicines proposed in the application are recommended in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guidelines (8).
1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children.

2. Application to review the therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EMLc for the treatment of schizophrenia and related psychotic disorders.
