Haloperidol

Section: 24. Medicines for mental and behavioural disorders > 24.1. Medicines for psychotic disorders

ATC codes: N05AD01

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A2Z
INN	Haloperidol
Medicine type	Chemical agent
List type	Core (EML) Complementary (EMLc)
Additional notes	The square box applies only to oral dose forms of haloperidol and chlorpromazine
Formulations	**Parenteral > General injections > IM:** 5 mg per mL in ampoule **Oral > Solid:** 2 mg ; 5 mg
EML status history	First added in 1977 (TRS 615) Changed in 1979 (TRS 641) Changed in 1987 (TRS 770) Changed in 2007 (TRS 950) Changed in 2009 (TRS 958) Changed in 2013 (TRS 985) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	chlorpromazine (ATC codes: N05AA01) Oral > Liquid: 25 mg per 5 mL (hydrochloride) Oral > Solid: 100 mg (hydrochloride)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Haloperidol
DrugBank	Haloperidol

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 (oral formulations only) 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.

Background

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.

Public health relevance

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. Psychotic disorders are very rare in childhood. The prevalence of the onset of psychotic symptoms before 13 years of age has been estimated to be 100 times lower than the adult form of the disorder (2). Due to the scarcity of definitive epidemiological studies, the true prevalence is likely to be even less (3,4). Two studies investigating rates of childhood neuropsychiatric disorders in Sweden and North Dakota (United States) found the prevalence of childhood-onset schizophrenia to be 1.6 per 100 000 children and 1.9 per 100 000 children, respectively (5–7). The largest study on childhood-onset schizophrenia to date, involving 1400 national referrals to the United States National Institute of Mental Health over 10 years, identified 260 children with psychosis of whom only 71 met the criteria for childhood-onset schizophrenia at study entry (8). Beyond schizophrenia, psychotic symptoms often represent an ancillary manifestation of other psychiatric conditions (e.g. major depression, bipolar disorder or psychosis not otherwise specified). A study comprising all types of psychiatric and child-guidance services in three large clinics in Germany subdivided childhood psychoses into four diagnostic groups: schizophreniform disorder, affective psychosis, typical non-schizophrenic child and adolescent psychosis and atypical psychosis. The analysis of the distribution of age at onset defined by age at first contact for the four diagnostic categories until the age of 15–18 years showed that first contacts for schizophrenia, affective psychoses or unspecified psychoses become visible in the age group of 12–15 years, followed by a steep increase in the next age group (9). Major depression may occur in 1% of children (10,11), whereas bipolar disorder occurs in 1% to 2% of adolescents (12,13). Mood disorders with psychosis are considerably rarer in children. The prevalence of psychosis not otherwise specified and bipolar disorder in children is hard to ascertain because of controversy about validity. More generally, transitory psychotic experiences may be triggered by various

psychiatric conditions. Finally, psychotic symptoms have been associated with, or are secondary to, a wide variety of medical disorders. Studies on adults show that about 3% of new-onset presentations of psychosis can be attributed to a medical condition (14). Therefore, before making a diagnosis of a primary psychotic disorder, secondary causes should be ruled out or, if necessary, adequately treated. Subclinical psychotic experiences may be more common and are usually benign, as in 75–90% of cases they spontaneously remit over time (13). ======= 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. About 24 million people in the world are estimated to have schizophrenia (2). The prevalence of schizophrenia ranges from 0.2% to 0.4% across countries, while its incidence is reported to be 18.7 per 100 000 person-years (3). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable specifically to schizophrenia spectrum disorders. Schizophrenia is also associated with relevant direct and indirect healthcare costs, and it is considered the costliest mental health condition per person globally (2,4). People with schizophrenia have a life expectancy about 14 years lower than the general population (5).

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 (31–33), 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. ======= 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.

Cost / cost effectiveness

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. Not applicable.

WHO guidelines

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders do not include any treatment recommendations for psychotic disorders in children (37). Similarly, other national and international guidelines do not include specific treatment recommendations for children, with most referring only to the adolescent population. ======= 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).

Availability

1. Application for deletion of chlorpromazine and haloperidol from the EMLc for the treatment of psychotic disorders in children. Chlorpromazine and haloperidol are available globally, however specific data on availability are not considered relevant for the proposal to delete them from 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 proposed medicines are available in branded and generic forms.

Other considerations

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. In consideration of a separate application at the meeting, the Expert Committee recommended the deletion of chlorpromazine immediate-release injection from the core list of the EML.

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

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2013 (WHO Technical Report Series, No. 985; https://apps.who.int/iris/handle/10665/112729, accessed 6 October 2023).
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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.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).
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