Fluphenazine

Essential medicine status

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

ATC codes: N05AB02

Indication	Schizophrenia or other primary psychotic disorders ICD11 code: 6A2Z
INN	Fluphenazine
Medicine type	Chemical agent
List type	Core
Formulations	**Parenteral > General injections > IM:** 25 mg per mL in ampoule (decanoate) ; 25 mg per mL in ampoule (enanthate)
EML status history	First added in 1977 (TRS 615) Changed in 1979 (TRS 641) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	haloperidol decanoate (ATC codes: N05AD01) zuclopenthixol decanoate (ATC codes: N05AF05)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Fluphenazine
DrugBank	Fluphenazine

Expert Committee recommendation

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

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

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

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

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

Not applicable.

WHO guidelines

The medicines proposed in the application are recommended in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guidelines (8).

Availability

The proposed medicines are available in branded and generic forms.

Other considerations

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. 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).
2. World mental health report: Transforming mental health for all. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/356119, accessed 6 October 2023).
3. Jongsma HE, Turner C, Kirkbride JB, Jones PB. International incidence of psychotic disorders, 2002-17: a systematic review and meta-analysis. Lancet Public Health. 2019;4(5):e229–e44.
4. Christensen MK, Lim CCW, Saha S, Plana-Ripoll O, Cannon D, Presley F, et al. The cost of mental disorders: a systematic review. Epidemiol Psychiatr Sci. 2020;29:e161.
5. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017;4(4):295–301.
6. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394(10202):939–51.

7. Leucht S, Chaimani A, Krause M, Schneider-Thoma J, Wang D, Dong S, et al. The response of subgroups of patients with schizophrenia to different antipsychotic drugs: a systematic review and meta-analysis. Lancet Psychiatry. 2022;9(11):884–93.
8. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Third edition. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374250, accessed 21 November 2023).