M E M O R A N D U M

From:	Director, MSD	**To:**	Director, HPS	**Date:**	14 Dec 2022
Our ref:		**Attention:**			
Your ref:		**Through:**	The Secretary of the Expert Committee on Selection and Use of Essential Medicines		
Originator:	Dr M. van Ommeren, MHE	**Subject:**	***PROPOSAL FOR REVISING THE SQUARE BOXES ASSOCIATED WITH HALOPERIDOL, CHLORPROMAZINE AND FLUPHENAZINE DECANOATE/ENANTATE IN THE WHO MODEL EML***		

Pharmacological options to treat psychotic disorders in the current WHO Model List of Essential Medicines (EML) (section 24.1) include **haloperidol, chlorpromazine, fluphenazine enantate/decanoate,** and **risperidone**.

While risperidone is the only representative of second-generation antipsychotics, haloperidol, chlorpromazine, and fluphenazine enantate/decanoate are marked with a square box symbol indicating that any FGA can be considered as a valid therapeutic alternative to them.

According to the most recent and high-quality meta-analytical evidence on both the acute and maintenance treatment of schizophrenia-spectrum disorders (1, 2), there are differences between FGAs in terms of efficacy, tolerability, and certainty of evidence. These differences have been shown both for oral and long-acting formulations. Therefore, we suggest restricting the square boxes associated to haloperidol, chlorpromazine, and fluphenazine decanoate/enantate to a selection of FGAs. To do so, we examined two high-quality network meta-analyses (1, 2) and reviewed the evidence on FGAs according to the following criteria:

(a) demonstrating better efficacy in comparison with placebo for acute treatment and/or maintenance treatment, considering the effect size as clinically meaningful when the confidence interval includes a standardized mean difference ≥0.3 for continuous outcomes (1) or a risk ratio ≤ 0.6 for dichotomous outcomes (2);

(b) having a moderate-to-high certainty of evidence according to the GRADE/CINeMA approach for acute or maintenance treatment, or both.

The following FGAs survived the selection process: **oral chlorpromazine, haloperidol,** and **long-acting haloperidol decanoate, fluphenazine enantate/decanoate,** and **zuclopenthixol decanoate**. Of relevance, when compared head-to-head, no statistical differences emerged with FGAs already included in the WHO EML. In addition, different side effects profiles emerged, although such tolerability outcomes were sparsely reported and are probably imprecise. In general, chlorpromazine showed a higher risk of weight gain and anticholinergic side effects compared to haloperidol, but its risk of extrapyramidal symptoms, akathisia, and hyperprolactinaemia was lower. Perphenazine showed a lower risk of sedation compared to both haloperidol and chlorpromazine, but data on other side effects was lacking.

Another relevant shortcoming is that, in the current version of the WHO EML, both oral haloperidol and chlorpromazine are marked with a square box indicating any FGA as a therapeutic alternative, which is redundant.

Request

On this basis, we argue that the following changes should be carefully considered:

- Among oral FGAs, maintaining only **haloperidol**, marked with a "restricted" square box indicating **chlorpromazine** therapeutic alternative;
- Among long-acting FGAs, maintaining **fluphenazine enantate/decanoate**, marked with a "restricted" square box indicating **haloperidol decanoate** and **zuclopenthixol decanoate** as therapeutic alternatives.

For FGAs not already included in the EML, we suggest considering the following doses and formulations:

- **haloperidol decanoate** (3): solution for injection ampoules: 50, 100 mg/mL, with initial doses of 25-150 mg every 4 weeks, and maintenance doses of 50-300 mg every 4 weeks;
- **zuclopenthixol decanoate** (4): solution for injection ampoules: 200, 500 mg/mL, with an initial test dose of 100 mg, and maintenance doses of 200-500 mg every 1 to 4 weeks, which can be further increased up to a maximum of 600 mg/weekly.

The indicated FGAs are generally considered cost-effective, are broadly available as generics, and are included in many national formularies and pharmacopoeias.

Of relevance, the Guidelines Development Group of WHO Mental Health Gap Action Programme (mhGAP) revision is considering recommending these medications as representative of FGAs for the treatment of schizophrenia and related psychoses in the forthcoming update of the mhGAP Guideline. It is expected that these recommendations on FGAs will be approved by the WHO Guidelines Review Committee by the time of the next meeting of the Expert Committee on the WHO EML.

Conclusions

We suggest restricting the FGAs currently considered in the section 24.1 of the EML to the aforementioned selection of medicines. Our proposal is based on the best-quality evidence currently available, and it is consistent with the forthcoming update of the mhGAP Guideline.

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