

A.24	Paliperidone, risperidone LAI
Does the application adequately address the issue of the public health need for the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Schizophrenia and psychotic disorders are major drivers of the global burden of disease, as measured in prevalence, disability-adjusted life-years, and years lived with disability.</p> <p>Pharmacological treatment of schizophrenia and related disorders from the early phases of disease may represent a key point for preserving neurocognitive abilities, delay the progression towards chronic functional deterioration, possibly resulting in better life conditions. Improving adherence to mental health therapies is important and long-acting formulations may increase compliance and make easier treatment dose control.</p>
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	<p>This Application regards the inclusion of risperidone long-acting injection and paliperidone palmitate 1-month long-acting injection for schizophrenia and related disorders.</p> <p>Paliperidone and risperidone share similar chemical structure and pharmacological and clinical profiles.</p> <p>Only fluphenazine (decanoate or enanthate) is currently listed as long-acting antipsychotics. Fluphenazine is listed with a square box, meaning that other first-generation long-acting antipsychotics may be used, for instance: haloperidol decanoate, zuclopenthixol decanoate.</p> <p>Several shortages of fluphenazine decanoate and other first generation antipsychotics occurred at the global level due to chain-production challenges. This represents a major threat for people requiring regular treatment over long periods of time.</p>
Have all important studies and all relevant evidence been included in the application?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p> <p>The Application reports a comprehensive and up-to-date review of the available studies.</p>

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?

- ☒ Yes
☐ No
☐ Not applicable

Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).

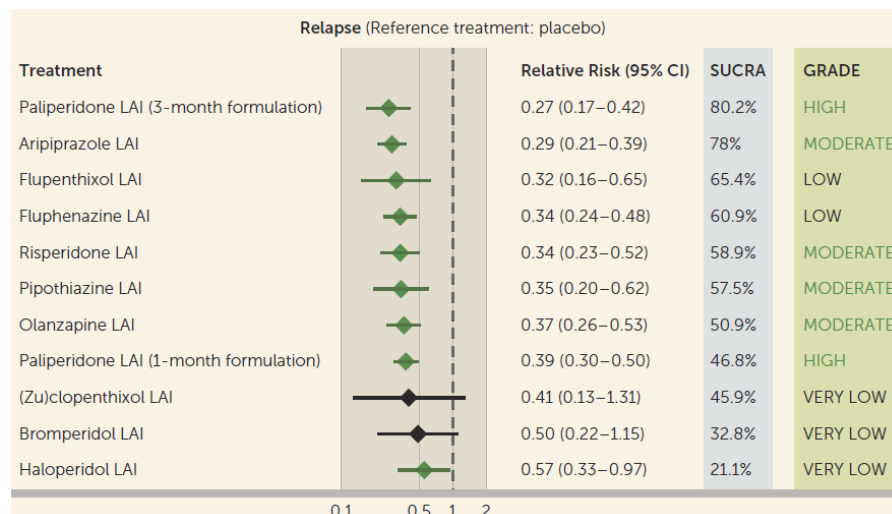
Benefit compared to oral medications

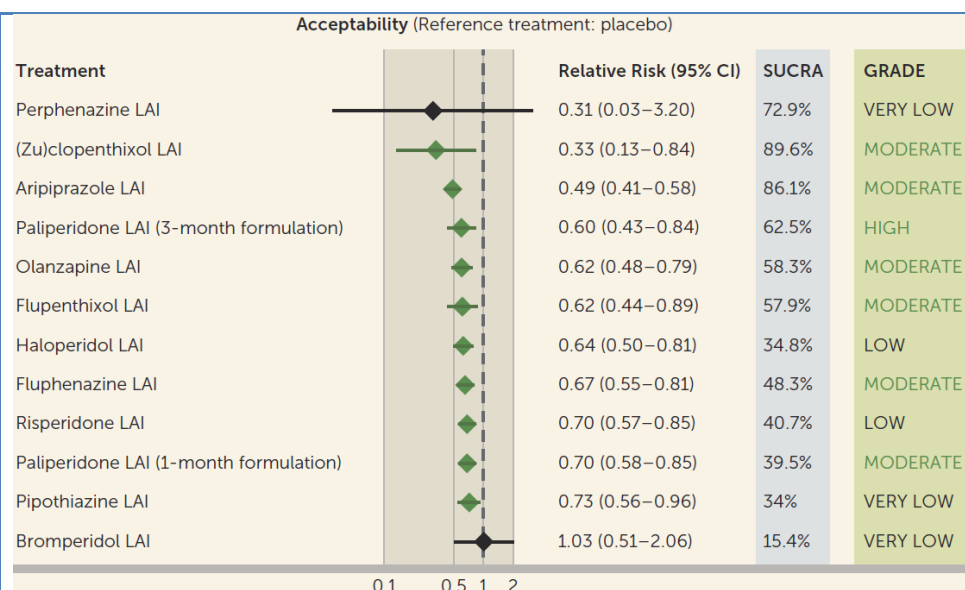
A recent systematic review (last search date March 2020) compared long acting and oral antipsychotics (Kishimoto 2021). The use of long-acting agents provided a significant effect on the likelihood of hospitalisation or relapse (RCTs; 29 studies, risk ratio [RR] 0.88 [95% CI 0.79–0.99], cohort studies (44 studies, RR 0.92 [0.88–0.96]), and pre-post studies (28 studies, RR 0.44 [0.39–0.51]).

Although not all the studies reported a benefit, these results might be especially meaningful for the population with an history of good response to an oral-antipsychotic but relapse due to medication nonadherence (Lauriello 2021).

Comparisons among long-acting medications

A network meta-analysis (last search June 2020) assessed the differential efficacy and acceptability of long-term antipsychotics among people with nonaffective psychoses (Ostuzzi 2021). Seventy-eight studies on 12 different antipsychotics for a total of more than 11,000 participants assessed one or more outcomes of interest: study-defined relapses and treatment discontinuation (acceptability). Most long-term antipsychotics were superior to placebo in preventing relapse and more acceptable.





The authors stated that as paliperidone (3-month and 1-month formulations), aripiprazole, and olanzapine were supported by moderate to high certainty of evidence in both primary outcomes, they can be regarded as reasonable first-line maintenance treatments in people with schizophrenia and related nonaffective psychosis.

Paliperidone palmitate 3-month long-acting is NOT included in this Application, given its recent introduction on the market and the methodological concerns affecting its pivotal trial.

The network meta-analysis did not show any difference in relapses or acceptability between paliperidone or risperidone and long acting fluphenazine.

Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

Most of the studies were conducted in high income countries. In setting where regular clinical follow-up is not easily established and maintained bi-monthly or monthly administration of long-acting antipsychotics may allow optimal medical care for maintenance treatment.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?

- ☒ Yes
☐ No
☐ Not applicable

Comments:

The choice of an antipsychotic is often influenced by its side effect profile and its match with the patient's clinical status and vulnerabilities.

Common side effects associated with first generation antipsychotics include extrapyramidal symptoms, tardive dyskinesia, hyperprolactinemia, neuroleptic malignant syndrome, QT prolongation, sudden death.

The safety profile of oral and long-acting formulations appears to be similar.

Paliperidone (1-month formulation) was less tolerable than placebo, while there were no differences between other long-acting antipsychotic and placebo (Ostuzzi 2021).

Specific side effects of paliperidone and risperidone include weight gain, extrapyramidal symptoms, hyperprolactinaemia. Paliperidone is also associated with QTc prolongation and sedation.

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p>In general, the benefit risk ratio of long-term antipsychotics in people with psychotic disorders (including schizophrenia) is favourable.</p> <p>They may represent a valuable option compared to oral medication, especially in context where treatment compliance may be suboptimal.</p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>Overall, the quality of evidence supporting the use of the long-acting paliperidone and risperidone ranges from moderate to high.</p> <p>The main limitation is the high number of placebo-controlled studies that may suffer from intrinsic limitations and do not provide direct evidence on comparative effectiveness among treatments.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Risperidone long-acting (Risperdal® Consta®) is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperdal® Consta®, a SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety needles for intramuscular injection. Therefore, this product requires a procedure of “reconstruction” which should be carefully followed for safety reasons and to avoid settling of the microspheres and/or contamination. The entire dose pack should be stored in the refrigerator (36°- 46°F; 2°- 8°C) and protected from light. If refrigeration is unavailable, Risperdal® Consta® can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration.</p> <p>In some low-and middle-income settings and in humanitarian contexts, these logistical constraints and the need for trained health caregivers may seriously hamper the use of long-acting risperidone.</p>
<p>Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Risperidone long-acting approved for</p> <p>FDA</p> <ul style="list-style-type: none"> • Schizophrenia • Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder <p>EMA</p> <ul style="list-style-type: none"> • maintenance treatment of schizophrenia in people currently stabilized with oral

	<p>antipsychotics</p> <p>Available also in Argentina; Australia; Brazil; Canada; Chile; China; Japan; Korea; New Zealand; Russia; Uruguay; United Kingdom; Switzerland</p> <p>Paliperidone long-acting approved for</p> <p>FDA</p> <ul style="list-style-type: none"> • schizophrenia • schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants <p>EMA</p> <ul style="list-style-type: none"> • maintenance treatment of schizophrenia in adults whose disease has already been stabilized on treatment with paliperidone or risperidone <p>Available also in Argentina; Australia; Brazil; Canada; Chile; China; Japan; Korea; New Zealand; Russia; United Kingdom; Switzerland.</p>
<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>World Health Organization (WHO). mhGAP Intervention Guide (Version 2.0) for mental, neurological and substance use disorders in non-specialized health settings. World Health Organization; 2016. Available: https://www.who.int/publications/i/item/mhgap-intervention-guide---version-2.0</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>Both medicinal products are marketed by Janssen-Cilag.</p> <p>Second-generation long-acting antipsychotics are currently marketed only under trade names, with notably higher costs as compared to first-generation long-acting antipsychotics, for which generics are available. In general, evidence on the cost-effectiveness of long-acting antipsychotics in real-world settings are heterogeneous in terms of population and setting analyzed, as well as methodology employed make it difficult to draw firm conclusions. However, considering the minor differences in efficacy it is unlikely that second-generation long-acting antipsychotics are cost effective in most of the global settings.</p> <p>According to the Application and the Medicine Patent Pool, the primary patents have been already expired for both paliperidone and risperidone while secondary patents - that prevent the marketing of generics – will expire in 2021 (risperidone) and 2028 (paliperidone).</p> <p>The production of generics with lower prices should be promoted in order to increase worldwide availability and reduce cost burden.</p>
<p>Any additional comments</p>	<p>Other Long-acting injectable antipsychotics</p> <p>First generation</p> <ul style="list-style-type: none"> • Fluphenazine decanoate • Flupentixol decanoate • Pipotiazine palmitate • Zuclopenthixol decanoate • Haloperidol decanoate

	<p>Second generation</p> <ul style="list-style-type: none"> • Aripiprazole extended release • Aripiprazole lauroxil • Olanzapine pamoate
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	<p>Long-acting antipsychotics are a valuable treatment option to increase adherence to treatments and reduce relapse in adults with schizophrenia and related disorders. Long-acting medications might be particularly useful in low-resource settings, where many factors might hamper regular monitoring and follow-up of individuals with psychosis.</p> <p>The added value of the second-generation long-acting antipsychotics (paliperidone and risperidone) over first-generation alternatives already listed appears to be minimal. However, the uncertainty of future availability of fluphenazine poses serious concerns and the inclusion of other agents may be relevant. Moreover, the availability of agents with a different side effect profile may support the selection of one treatment over another considering patient's clinical status and vulnerabilities.</p> <p>Therefore, this Reviewer supports the inclusion of long-acting formulations of paliperidone and risperidone.</p> <p>The Expert Committee may wish to consider one of the following options:</p> <p>-include long-acting paliperidone with a restricted square box (□), as representative of the group of second-generation antipsychotics (risperidone, aripiprazole, olanzapine).</p> <p>Or</p> <p>-include long-acting paliperidone and risperidone under the square box of fluphenazine, as a possible alternative with a similar benefit-risk profile but higher costs.</p> <p>The inclusion of second-generation antipsychotics in the Model List should be accompanied with measures to increase manufacturing capacity and generic production, to reduce the cost burden.</p>
References (if required)	<p>Kishimoto T Hagi K Kurokawa S Kane JM Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. <i>Lancet Psychiatry</i>. 2021;8(5):387-404.</p> <p>Lauriello G, Campbell AR. Pharmacotherapy for schizophrenia: Long-acting injectable antipsychotic drugs. <i>Uptodate</i> 2021.</p> <p>Ostuzzi G, Bertolini F, Del Giovane C, et al. Maintenance treatment with long-acting injectable antipsychotics for people with nonaffective psychoses: a network meta-analysis <i>Am J Psychiatry</i> 2021; 178:424–436</p>