PROPOSAL FOR THE ADDITION OF RISPERIDONE LONG-ACTING INJECTION AND PALIPERIDONE PALMITATE 1-MONTH LONG-ACTING INJECTION FOR THE TREATMENT OF ADULTS WITH SCHIZOPHRENIA AND RELATED CHRONIC PSYCHOTIC DISORDERS TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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GENERAL ITEMS

1. Summary statement of the proposal for inclusion, change or deletion.

In this application, we propose the addition of (a) risperidone long-acting injection and (b) paliperidone palmitate 1-month long-acting injection to the core list of the WHO Model List of Essential Medicines (EML), section 24.1 "Medicines for mental and behavioural disorders >> Medicines used in psychotic disorders", with the indication of maintenance treatment of adults with schizophrenia or related chronic psychotic disorders.

This proposal is based on the following elements:

a. In the last decade, the scientific evidence supporting long-acting antipsychotics (LAIs) has grown exponentially. These formulations are increasingly recognized as important to improve adherence to treatments and reduce relapse in adults with schizophrenia and related disorders. Maintenance treatment with long-acting antipsychotics is increasingly used by clinicians and individuals suffering from psychosis as a valuable treatment option;
b. 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. Also, during the ongoing SARS-CoV2 pandemic emergency, long-acting formulations have represented an important treatment option, considering their practicality in reducing the frequency of face-to-face appointments, as pointed out in by the World Health Organization's "Maintaining essential health services: operational guidance for the COVID-19 context interim guidance"[1] and the Inter-Agency Standing Committee's "Guidance on Operational considerations for Multisectoral Mental Health and Psychosocial Support Programmes during the COVID-19 Pandemic"[2];
c. Currently, only fluphenazine decanoate or enantate is the long-acting antipsychotic reported on the 21st WHO EML. The availability of fluphenazine decanoate/enantate at a global level is erratic due to chain-production challenges, which represent a major threat for people requiring regular treatment over long periods of time. Some years ago the production of fluphenazine decanoate long-acting (Moditen®/Modecate®) was discontinued by the manufacturer (Sanofi) due to manufactory and supply problems[3], and it is uncertain whether its production will continue in the future, or whether it will be limited to a restricted number of manufacturers and countries. This challenge may

[1] Chapter 2.2.3: "[…] introduce use of longer prescription periods involving either expanded take-home practices (e.g. for methadone or buprenorphine treatment, sustained release antiseizure medicines, or neuroleptic depot with informed consent)". Available: https://apps.who.int/iris/handle/10665/332240
[2] Page 16: "Develop a clear strategy for the administration of long-acting antipsychotic medication. This may involve changing the interval of administration to avoid travel during periods of high contagion risk, or administering the medication during home visits instead of at the health facility". Available: https://interagencystandingcommittee.org/iasc-reference-group-mental-health-and-psychosocial-support-emergency-settings/iasc-guidance
[3] https://www.kmptformulary.nhs.uk/media/1037/disontinuation-of-fluphenazine-modecate-im.pdf

be particularly severe for low-resource settings, where no alternative options may be available and disruption of the drug supply chain may have harmful clinical consequences;

d. Fluphenazine decanoate/enantate is included in the EML with a square box (□), meaning that a similar clinical performance is expected within the group of first-generation long-acting antipsychotics, which includes haloperidol decanoate, zuclopenthixol decanoate, perphenazine enanthate, pipotiazine palmitate, bromperidol decanoate, and flupenthixol decanoate. However, most of these medications are rather outdated, out of production, or rarely used in clinical practice, with the exception of haloperidol decanoate and zuclopenthixol decanoate;
e. Even if fluphenazine decanoate/enantate or other first-generation long-acting antipsychotics were available, the addition of a second-generation long-acting antipsychotics to the EML would be helpful as individual treatment response vary in terms of both desirable and undesirable outcomes, and experts and guidelines suggest to tailor treatment choices based on individual characteristics (1-4);
f. According to the most recent, high-quality meta-analytical evidence, both risperidone long-acting and paliperidone palmitate 1-month long-acting are overall effective and acceptable, with no relevant differences compared to other long-acting antipsychotics. Further, the certainty of evidence supporting these medications is moderate-to-high according to the GRADE methodology;
g. Paliperidone and risperidone are very similar chemical compounds, as the former is the principal active metabolite of the latter, and have very similar pharmacological and clinical profiles. Paliperidone palmitate 1-month long-acting can be initiated in people already clinically stabilized with oral paliperidone or oral risperidone. The latter is included, as oral antipsychotic, in the 21st WHO EML and is one of the most available antipsychotic medicines in the world. Therefore, many people requiring a switch to a long-acting injectable antipsychotic may already be taking oral risperidone and switching to long-acting paliperidone or long-acting risperidone would be a safer and more conservative step to take than switching to long-acting fluphenazine;
h. Costs and worldwide availability of long-acting antipsychotics might notably vary. Although currently both risperidone long-acting and paliperidone palmitate 1-month long-acting are marketed by Janssen-Cilag with the branded names of Risperdal® Consta® and Invega® Sustenna®/Xeplion®, respectively, most of the patents that prevent the marketing of generics are already expired, and most of the remaining will expire soon. From this standpoint, their addition to the EML list would certainly booster an effort to the production of generics with lower prices and increased worldwide availability.

2. Relevant WHO technical department and focal point.

Dr. Mark van Ommeren; WHO Department of Mental Health & Substance Use

Dr. Fahmy Hanna; WHO Department of Mental Health & Substance Use

3. Name of organizations consulted and supporting the application.

Dr. Peter Ventevogel, Senior Mental Health Officer from the United Nations High Commissioner for Refugees (UNHCR), was consulted as an expert in the field of psychiatric interventions in humanitarian/low-resource settings. He supports the inclusion of paliperidone palmitate 1-month long-acting to the EML.

Patent information courtesy of the Medicines Patent Pool (reference person: Amina Maillard, Patent Information Manager).

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

The ATC code for risperidone long-acting is N05AX08 and the INN code is 6085.

The ATC code for paliperidone palmitate is N05AX13 and the INN code is 7977.

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Risperidone long-acting: Powder and solvent for prolonged-release suspension (microspheres) for injection 12.5 mg; 25 mg, 37.5 mg, 50 mg.
Paliperidone palmitate 1-month long-acting: prolonged release suspension for injection 25 mg, 50 mg, 75 mg, 100 mg, 150 mg.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We are proposing the addition of the individual medicines “risperidone long-acting injection” and “paliperidone palmitate 1-month long-acting injection” to section 24.1 “Medicines for mental and behavioural disorders >> Medicines used in psychotic disorders”.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

We are requesting the addition of the medicines:

- **Risperidone long-acting injection** for the maintenance treatment of schizophrenia and related chronic psychoses in adults, with a dose regimen comprised between 12.5 mg and 50 mg every two weeks;
- **Paliperidone palmitate 1-month long-acting injection** for the maintenance treatment of schizophrenia and related chronic psychoses in adults, with a dose regimen comprised between 25 mg and 150 mg every four weeks.

In general, long-acting medications represent a promising innovation in different fields of medicine, considering their sustained and controlled release. Long-acting formulations make it easier to control treatment dose, and reduce the risk of taking medicine incorrectly. Long-acting formulations are increasingly used in the fields of contraception, harm reduction, diabetes, and are rapidly developing also in the field of infectious diseases[4].

Several systematic reviews of both randomized clinical trials and observational studies showed that long-acting antipsychotics might have advantages as compared to oral antipsychotics in the maintenance treatment of schizophrenia and other chronic non-affective psychoses, although results from different study designs might not be fully consistent:

- Kishimoto and colleagues (5) pooled data from 21 randomized trials (including 4950 participants) comparing oral and long-acting antipsychotics in both in- and out-patients with schizophrenia, with a follow-up of at least 6 months. The meta-analysis found no differences between the two formulations in terms of relapse rate (relative risk (RR) 0.93; 95% confidence interval (CI) 0.80 to 1.08; I^2=58%; 21 studies; 4950 participants);
- Kishimoto and colleagues (6) retrieved 42 prospective and retrospective cohort studies (including 101,624 participants) comparing oral and long-acting antipsychotics, with a follow-up of at least 6 months. Meta-analyses showed that long-acting performed better than oral antipsychotics in terms of "hospitalization rate" (number of hospitalizations divided by person-years at risk; RR 0.85, 95% CI 0.78 to 0.93; I^2=94.9%, 68,009 person-years; 15 studies) and "all-cause discontinuation" (RR 0.78, 95% CI 0.67 to 0.91; I^2=93%; 10 studies; 37,293 persons), while no differences emerged in terms of "hospitalization risk" (number of persons who had ≥1 hospitalization divided by the number of patients at risk; RR 0.92, 95% CI 0.84 to 1.00; I^2=84.6%; 33 studies, 51,733 persons);

[4] https://medicinespatentpool.org/what-we-do/long-acting-hub/

- Another meta-analysis by Kishimoto and colleagues (7) retrieved 25 observational, mirror-image studies (including 5940 participants), comparing oral and long-acting antipsychotics in adults with schizophrenia, of at least 12 months of duration (≥6 months each on oral and long-acting antipsychotic treatment). The meta-analysis showed a clear benefit for long-acting antipsychotics in reducing the risk of hospitalization (RR 0.43, 95% CI 0.35 to 0.53; I^2=87.6%; 16 studies; 4066 participants), as well as the number and the length of hospitalizations;
- Olaguniu and colleagues (8) pooled data from 19 randomized studies (including 8616 adults with schizophrenia) assessing functional outcomes. The meta-analysis showed second-generation long-acting antipsychotics (no data were available for first-generation antipsychotics) to be superior to both placebo (standardized mean difference (SMD) 0.39; 95% CI 0.32 to 0.47; I^2=0%; 2862 participants; 9 studies) and oral antipsychotics (SMD 0.16; 95% CI 0.01 to 0.31; I^2=77%; 3540 participants; 10 studies) for improved psychosocial function. This superiority was maintained in both short- and long trials.

Generally, these systematic reviews and meta-analyses pooled together different long-acting and oral medications, preventing to draw conclusions on the comparative efficacy and acceptability of individual medications.

Long-acting antipsychotics are broadly recognized by researchers (9, 10) and national and international guidelines (3, 11-18) as a treatment option to improve adherence to treatments and reduce the risk of multiple relapses and hospitalizations, even from the early phases of the disease (Table 1).

According to WHO guidelines ***"In people with psychotic disorders (including schizophrenia) requiring long-term antipsychotic treatment, depot antipsychotics can be offered instead of oral medications as part of a treatment plan. […] Patients and carers should be offered clear and accessible information in a suitable format regarding the use and possible side effects of oral versus depot preparations"*** (16, 19). This is consistent with the 21st WHO EML, which include fluphenazine (enantate or decanoate) as a representative of first-generation long-acting antipsychotics (20). In general, existing guidelines agree in suggesting long-acting antipsychotics **when this is preferred by patients or when relevant problems of adherence are detected**. Most guidelines do not provide clear indications on which antipsychotic to choose. According to the NICE and the APA guidelines, the same criteria used for the choice of oral antipsychotics should be employed.

Table 1. Excerpts from national and international guidelines on the pharmacological treatment of schizophrenia and other chronic psychoses

Source	Year	Excerpts from the guideline
The Schizophrenia Patient Outcomes Research Team (PORT)	2009	▪ Long-acting injectable (LAI) antipsychotic medication should be offered as an alternative to oral antipsychotic medication for the maintenance treatment of schizophrenia when the LAI formulation is preferred to oral preparations. The recommended dosage range for fluphenazine decanoate is 6.25–25 mg administered every 2 weeks and for haloperidol decanoate is 50–200 mg administered every 4 weeks, although alternative dosages and administration intervals equivalent to the recommended dosage ranges may also be used. The recommended dosage range for risperidone long-acting injection is 25–75 mg administered every 2 weeks.
World Federation of Societies of Biological Psychiatry (WFSBP)	2013	▪ There is good evidence to support the use of long-acting injectable olanzapine (Category of evidence (A)/B, Recommendation grade (2)/3). It should be mentioned that we were not able to identify a comparator study between olanzapine pamoate and another depot antipsychotic. ▪ The postinjection delirium sedation syndrome needs to be considered as a possible severe side effect after every injection. ▪ Each injection should follow the rules of action described by the manufacturer and after each injection, a three hour observation period needs to be respected (Category of evidence C, Recommendation grade 4).
Scottish Intercollegiate Guidelines Network (SIGN)	2013	▪ Individuals with schizophrenia who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication. ▪ Service users should be given the option of oral or depot medication, in line with their preference.
The National Institute for Health and Care Excellence (NICE)	2014	▪ Consider offering depot/long-acting injectable antipsychotic medication to people with psychosis or schizophrenia: (a) who would prefer such treatment after an acute episode; (b) where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. ▪ When initiating LAI [...] take into account the same criteria recommended for the use of oral antipsychotic medication [...].
The Royal Australian and New Zealand College of Psychiatrists (RANZCP)	2016	▪ Long-acting injectable antipsychotic agents should be offered to patients early in the clinical course of schizophrenia. ▪ Consider the use of long-acting injectable antipsychotic medicines if: - the individual prefers a long-acting injectable medicine, - adherence has been poor or uncertain, - there has been a poor response to oral medication. ▪ Long-acting injectable antipsychotic agents, particularly second generation antipsychotics, provide an important treatment option in all phases of the disease for people whose adherence to oral treatment is poor.

WHO Mental Health Gap Action Programme (mhGAP), Version 2.0	2016	▪ Clinical situation: adherence to treatment is unsatisfactory Action: Consider depot/long-acting injectable antipsychotic medication as an option after discussing possible side effects of oral versus depot preparations (from Table 4, page 44). ▪ Depot antipsychotics should not be routinely prescribed to women with psychotic disorders who are planning a pregnancy, pregnant, or breastfeeding because there is relatively little information on their safety in this population
Canadian Schizophrenia Guidelines (CSG)	2017	▪ Patients should be given the option of oral or depot antipsychotic in line with their preference. ▪ […] a switch in formulation to a depot or LAI antipsychotic may represent the preferred strategy in an individual in whom antipsychotic nonadherence plays a clear role in acute exacerbations.
British Association of Psychopharmacology (BAP)	2020	▪ Patients should be offered the option of depot/long-acting injectable antipsychotic medication for maintenance treatment, given the evidence of lower risk of relapse. ▪ […] an alternative strategy to tackle poor adherence is the use of depot/LAI antipsychotic preparations, which make adherence transparent.
The American Psychiatric Association (APA)	2020	▪ APA suggests (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence. ▪ If a decision is made to initiate treatment with an LAI, aspects of medication selection are similar to those for selection of an oral medication in terms of considering prior response, prior tolerability, pharmacological considerations, and side-effect profiles.

Available guidelines do not provide information on additional requirements associated with long-acting use, including diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements, and skill levels of health care providers. In general, the administration of injectable long-acting antipsychotics is performed by health care professionals, and requires some technical precautions, as described in the EMA Annex III of these products[5].

From a feasibility and practicality standpoint, it is relevant to consider that:

- **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 (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration). 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**

[5] https://www.ema.europa.eu/en/documents/product-information/xeplion-epar-product-information_en.pdf; https://www.ema.europa.eu/en/documents/referral/risperdal-consta-article-30-referral-annex-i-ii-iii_en.pdf

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**. Do not expose unrefrigerated product to temperatures above 77°F (25°C)[6];

- **paliperidone palmitate long-acting** (Invega® Sustenna®) is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection; the kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle). **This product can be stored at room temperature** (25°C, 77°F), and excursions between 15°C and 30°C (between 59°F and 86°F) are permitted[7].

These elements might have relevant implications in terms of feasibility, in particular in low-resource/humanitarian contexts where refrigerators might not be available and there may be a lack of highly trained health providers.

WHO mhGAP provides generic information on how to safely introduce antipsychotics and monitor possible side-effects, including "monitoring weight, blood pressure, fasting sugar, cholesterol and ECG for persons on antipsychotics if possible". However, it should be noted that, usually, people initiating a long-acting antipsychotic are already under treatment with oral antipsychotics, and therefore changes to ongoing clinical monitoring are usually not required.

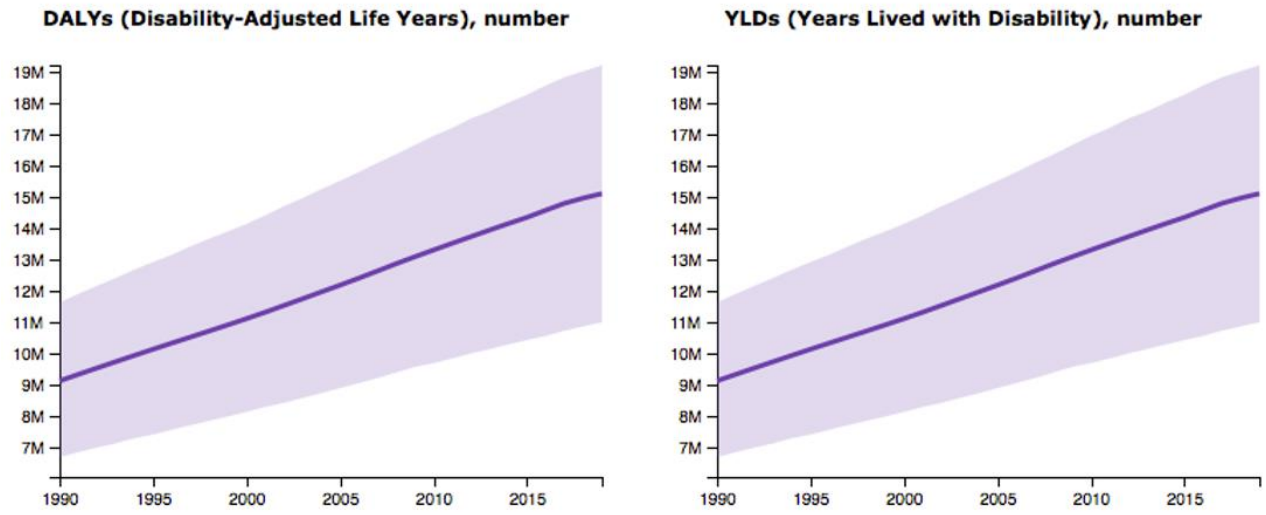
8. Information supporting the public health relevance.

Schizophrenia and related psychotic disorders are severe psychiatric conditions that have a profound effect on both the individuals affected and society. 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. More than 50% of individuals who receive a diagnosis have intermittent but long-term psychiatric problems, and around 20% have chronic symptoms and disability (21). The prevalence of schizophrenia typically ranges from 0.2 to 0.4% across countries. It is estimated that 20 million people in the world have schizophrenia (22) which translates to roughly 0.9% of the world's population. Incidence of non-affective psychoses were found to be 18.7 per 100 000 person-years (23). The burden of schizophrenia, as estimated by the Global Burden of Disease (GBD) 2017, contributes 12.66 (95% UI = 9.48 to 15.56) million disability-adjusted life years (DALYs) to burden of disease globally (24). Such a high degree of disability accounts for 1.1% of the total DALYs and 2.8% of years lived with disability (YLD) (25).

[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021346_s31_s35_s38_s39lbl.pdf
[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022264s023lbl.pdf

The GBD due to psychosis appears to be increasing over time. Figure 1 shows the trend in DALYs and YLDs due to Schizophrenia, between 1990 and 2020.

Figure 1. Global trend in DALYs and YLDs due to schizophrenia (both sexes, all ages) between 1990 and 2020 (graphs created using the GBD Results Tool, http://ghdx.healthdata.org/gbd-results-tool)



In addition to the large burden of disease caused by schizophrenia and related disorders directly, there is a well-known relationship between schizophrenia and stress-related non-communicable diseases (26). People with schizophrenia have a reduced life expectancy compared to the general population, calculated to be 14.5 years (27). While suicide explains some of this reduced life expectancy (28), it is now established that physical diseases account for the overwhelming majority of premature mortality (29, 30).

According to current evidence, regular pharmacological treatment from the early phases of disease may represent a key point for preserving neurocognitive abilities, for preventing structural brain changes, and for hindering the progression towards chronic functional deterioration, resulting in better life conditions and increased survival (31). However, treatment adherence is a major issue, considering that up to half of persons suffering from schizophrenia may not take their medications as prescribed and that only one out of three persons with schizophrenia are fully adherent to antipsychotic treatment (32, 33). It is worth noting that, among other factors, medication non-adherence is a relevant predictor of relapse (34).

Improving adherence to prescribed medicines is important in healthcare, as recently emphasized by the World Health Organization (35). There are a number of approaches that can be used to improve adherence. Patient and family psychoeducation is very important in providing a better understanding of the illness, its course and treatment, as well as the potential benefits and risks of treatment versus no treatment. It is often

difficult for people to understand the concept of prevention and the need to continue medication even long after symptoms have subsided.

Long-acting injectable antipsychotics were developed with the primary aim of addressing both hidden and overt non-adherence. There are well-known disadvantages of long-acting antipsychotics, including human rights concerns related to overuse, coercion and chemical constraints, lack of flexibility in dose adjustments, and the experience of pain at the injection site and, potential social stigma. There are also several potential advantages of a prescription of these formulations. First, as long-acting antipsychotics allow a complete tracking of the drug consumption, they may prevent the impact of the loss of doses of antipsychotics in early stages of the disease. Second, long-acting antipsychotics allow for avoiding daily administration, which may be perceived by the person as a practical advantage, and may minimize the risk of self-medication and harmful drug use. Third, considering experiences of an overall good balance of efficacy and tolerability in the long term, the need for de-stigmatizing LAIs and overcoming old misconceptions has been emphasized (36).

With surveys and trials suggesting their benefits and a dramatic reduction in the morbidity of schizophrenia (37-40), long-acting antipsychotics became widely adopted. The introduction of the oral second-generation antipsychotics (SGAs) brought claims of better tolerance and less severe side effects, they also have potential to prevent or reverse accelerated frontotemporal cortical grey matter decline, and to provide a greater degree of neuroprotection than first-generation antipsychotics (FGAs) (41, 42). The introduction of SGAs led to a decline in the use of LAI FGAs (43). However, it soon became clear that atypical characteristics did not bring better adherence rates with oral SGAs. The introduction of LAI SGAs allows psychiatrists once again to prescribe long-acting antipsychotics without losing any of the potential advantages of the SGAs (44).

It has been pointed out that the median value for treatment coverage in LMIC is estimated to be about 30% (45). This suggests that roughly two thirds (69%) of people with schizophrenia and related disorders in LMICs are not receiving adequate treatment. The treatment gap for schizophrenic disorders was larger in lower-income countries (89%) than in lower-middle-income (69%) and upper-middle-income countries (63%) (LMICs). The size of the treatment gap shows a significant negative association with the prevalence of schizophrenic disorders in the general population; gross national income; the availability of psychiatric hospital beds; the number of psychiatrists per 100,000 population and the number of nurses in mental health facilities per 100,000 population (45). Increasing service coverage to people with severe mental disorders including psychosis by 20% is one of the main targets of the WHO's "Comprehensive Mental Health Action Plan 2013-2020 (extended to 2030)"[8].

The introduction of risperidone long-acting and paliperidone palmitate 1-month long-acting in the WHO Model List of Essential Medicine could improve the capability of national health care systems to provide

[8] Source: http://www.emro.who.int/mnh/mental-health-action-plan/index.html

accessible and rational use of SGA LAIs to treat schizophrenia and related psychotic disorders, increase the service coverage for people with chronic psychoses and reduce the public health burden associated with these conditions.

9. Review of benefits: summary of evidence of comparative effectiveness.

We searched electronic databases PubMed, CINHAL, CENTRAL, EMBASE, and Web of Science Core Collection for the most updated systematic reviews on the topic of long-acting antipsychotics' efficacy, acceptability, tolerability and safety in adults with schizophrenia and related chronic psychoses. The following terms were searched in the title/abstract: (schizophrenia OR schizoaffective OR psychosis OR psychotic) AND (long-acting OR depot OR inject* OR long-term treatment OR maintenance treatment) AND review. After having screened 1430 titles and abstracts, and subsequently 57 full-texts articles, we included four systematic reviews and meta-analyses (1, 36, 46, 47). Additional material, retrieved by revising the bibliography of included systematic reviews, or after the input of experts in the field, included four observational studies (48-51) and three commentaries (9, 10, 52). Finally, for the purposes of this application, we conducted a network meta-analysis comparing long-acting formulations in people with schizophrenia and related disorders, which has been recently accepted for publication in *The American Journal of Psychiatry*.

The new systematic review and network meta-analysis evaluated the comparative efficacy, acceptability and tolerability of long-acting antipsychotics in adults with chronic non-affective psychosis. Relative risks (RR) and standardized mean differences (SMD) were pooled using random-effects pairwise and network meta-analysis. The primary outcomes were relapse rate and all-cause discontinuation ("acceptability"). The quality of included studies was rated with the Cochrane Risk of Bias tool, and the certainty of pooled estimates with the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation) adapted for network meta-analysis by using the web-application CINeMA (Confidence in Network Meta-Analysis). For the primary outcomes, a treatment hierarchy was produced by means of surface under the cumulative ranking curve (SUCRA). The search included 78 randomized controlled trials, comprising 11,505 participants and 12 different LAIs. Characteristics of studies which contributed to the outcome "relapse" are reported in Table 2 and the network map is shown in Figure 3a.

In terms of relapse rate, the following LAIs (ordered from the largest to the smallest point estimate) were significantly more effective than placebo: paliperidone-LAI 3-monthly (relative risk 0.27; 95% confidence interval 0.17 to 0.42), aripiprazole-LAI (relative risk 0.29; 95% confidence interval 0.21 to 0.39), flupenthixol-LAI (relative risk 0.32; 95% confidence interval 0.16 to 0.65), fluphenazine-LAI (relative risk 0.34; 95% confidence interval 0.24 to 0.48), risperidone-LAI (relative risk 0.34; 95% confidence interval 0.23 to 0.52), pipothiazine-LAI (relative risk 0.35; 95% confidence interval 0.20 to 0.62), olanzapine-LAI (relative risk 0.37;

95% confidence interval 0.26 to 0.53), paliperidone-LAI 1-monthly (relative risk 0.39; 95% confidence interval 0.30 to 0.50) and haloperidol-LAI (relative risk 0.57; 95% confidence interval 0.33 to 0.97) (Table 3 and Figure 4). Head-to-head comparisons showed paliperidone-LAI 3-monthly, aripiprazole-LAI and fluphenazine-LAI and to be more effective than haloperidol-LAI (Table 3). No relevant heterogeneity emerged from pairwise comparisons (i.e., I^2>50%), and the network did not show significant overall heterogeneity (estimated between-studies standard deviation (SD)=0.07) and overall incoherence (design-by-treatment test, p=0.45). Intra-loop incoherence emerged for four loops, all of them involving placebo and haloperidol-LAI. Results of the network meta-analyses were consistent with results from pairwise meta-analyses, except for haloperidol-LAI versus placebo (favouring of the latter in the direct estimate) and fluphenazine-LAI versus haloperidol-LAI (not significant in the direct estimate). Generally, there was statistical agreement between direct and indirect estimates, except for four comparisons: fluphenazine-LAI, haloperidol-LAI and paliperidone-LAI 3-monthly versus placebo, and paliperidone-LAI 1-monthly versus paliperidone-LAI 3-monthly.

Paliperidone-LAI 3-monthly, aripiprazole-LAI and flupenthixol-LAI ranked best according to the mean SUCRA. Compared to placebo, the certainty of evidence was “high” for paliperidone-LAI 3-monthly and paliperidone-LAI 1-monthly, and “moderate” for aripiprazole-LAI, risperidone-LAI, pipothiazine-LAI and olanzapine-LAI. The certainty of evidence was “moderate” also for the comparison paliperidone-LAI 3-monthly vs. paliperidone-LAI 1-monthly, while it was “very low” or “low” for most comparisons due to “within study bias”, which includes high risk of reporting bias, attrition bias, and sponsorship bias (Figure 4). Results of sensitivity analyses generally confirmed those of the primary analysis, however, they suggested that placebo-controlled studies might have been responsible for most of the observed intra-loop incoherence. Further, statistical disagreement between direct and indirect estimates disappeared after removing placebo-controlled studies from the analysis.

Characteristics of studies which contributed to the outcome “acceptability” (all-cause discontinuation) are reported in Table 2 and the network map is shown in Figure 3b. In terms of acceptability, the following LAIs (ordered from the largest to the smallest point estimate) were significantly more acceptable than placebo: (zu)clopenthixol-LAI (relative risk 0.33; 95% confidence interval 0.13 to 0.84), aripiprazole-LAI (relative risk 0.49; 95% confidence interval 0.41 to 0.58), paliperidone-LAI 3-monthly (relative risk 0.60; 95% confidence interval 0.43 to 0.84), olanzapine-LAI (relative risk 0.62; 95% confidence interval 0.48 to 0.79), flupenthixol-LAI (relative risk 0.62; 95% confidence interval 0.44 to 0.89), haloperidol-LAI (relative risk 0.64; 95% confidence interval 0.50 to 0.81), fluphenazine-LAI (relative risk 0.67; 95% confidence interval 0.55 to 0.81), risperidone-LAI (relative risk 0.70; 95% confidence interval 0.57 to 0.85), paliperidone-LAI 1-monthly (relative risk 0.70; 95% confidence interval 0.58 to 0.85) and pipothiazine-LAI (relative risk 0.73; 95% confidence interval 0.56 to 0.96) (Table 3 and Figure 4). Head-to-head comparisons showed aripiprazole-LAI to be

significantly superior to bromperidol-LAI, fluphenazine-LAI, paliperidone-LAI 1-monthly, pipothiazine-LAI and risperidone-LAI (Table 2). Moderate heterogeneity was detected for three pairwise comparisons (olanzapine-LAI versus olanzapine-OS, placebo vs. haloperidol-LAI and fluphenazine-LAI versus phenothiazines OS), although the network did not show significant overall heterogeneity (estimated between-studies SD=0.08) and overall incoherence (design-by-treatment test, p=0.22). The test for intra-loop incoherence was statistically significant for the loop including placebo, haloperidol-LAI and paliperidone-LAI 1-monthly. Results of the network meta-analyses were consistent with those from pairwise meta-analyses, except for haloperidol-LAI and pipothiazine-LAI vs. placebo, and aripiprazole-LAI vs. paliperidone-LAI 1-monthly (not significant in the direct estimate). There was statistical agreement between direct and indirect estimates, except for haloperidol-LAI and paliperidone-LAI 1-monthly versus placebo. Among those LAIs significantly superior to placebo, (zu)clopenthixol-LAI, aripiprazole-LAI and paliperidone-LAI 3-monthly ranked best according to the SUCRA. Compared to placebo, the certainty of evidence was “high” for paliperidone-LAI 3-monthly and “moderate” for (zu)clopenthixol-LAI, aripiprazole-LAI, olanzapine-LAI, flupenthixol-LAI, fluphenazine-LAI and paliperidone-LAI 1-monthly. For most of the head-to-head comparisons, the certainty of evidence was “very low” or “low” due to “within study bias” and imprecision of results. Results of sensitivity analyses generally confirmed those of the primary analysis, however they suggested that placebo-controlled studies and older and smaller studies might have been responsible for most of the observed intra-loop incoherence, and that studies with high overall risk of bias also contributed to the overall incoherence of the network. Statistical disagreement between direct and indirect estimates disappeared after removing placebo-controlled studies from the analysis.

Table 2. Characteristics of randomized controlled trials included in each network of primary outcomes.

	Relapse network	**Acceptability network**
No. of studies	69	74
No. of people included	11,176	11,385
Mean age (range), years	40 (21.5 to 57.1)	40 (21.5 to 57.1)
Women, %	37.6%	36.9%
Mean follow-up, No. studies (%) 12 to 26 weeks 27 to 52 weeks 53 weeks or more	 22 (31.9%) 35 (50.7%) 12 (17.4%)	 26 (35.1%) 35 (47.3%) 13 (17.6%)
Blinding, No. studies (%) Double-blind Open-label Unclear/not reported	 52 (75.4%) 15 (21.7%) 2 (2.9%)	 15 (20.3%) 55 (74.3%) 4 (5.4%)
Year of publication, No. studies (%) Until 1989 1990 to 2009 2010 to 2019	 32 (46.4%) 18 (26.1%) 19 (27.6%)	 35 (47.3%) 20 (27%) 19 (25.7%)
Type of comparison, No. studies (%) LAI vs. placebo LAI vs. oral LAI vs. LAI LAI vs. oral vs. placebo	 18 (26.1%) 25 (36.2%) 25 (36.2%) 1 (1.5%)	 20 (27%) 24 (32.4%) 29 (39.2%) 1 (1.4%)
Setting, No. studies (%) Inpatients Outpatients Mixed Unclear/not reported	 15 (21.7%) 35 (50.7%) 14 (20.3%) 5 (7.3%)	 15 (20.3%) 38 (51.3%) 14 (18.9%) 7 (9.5%)

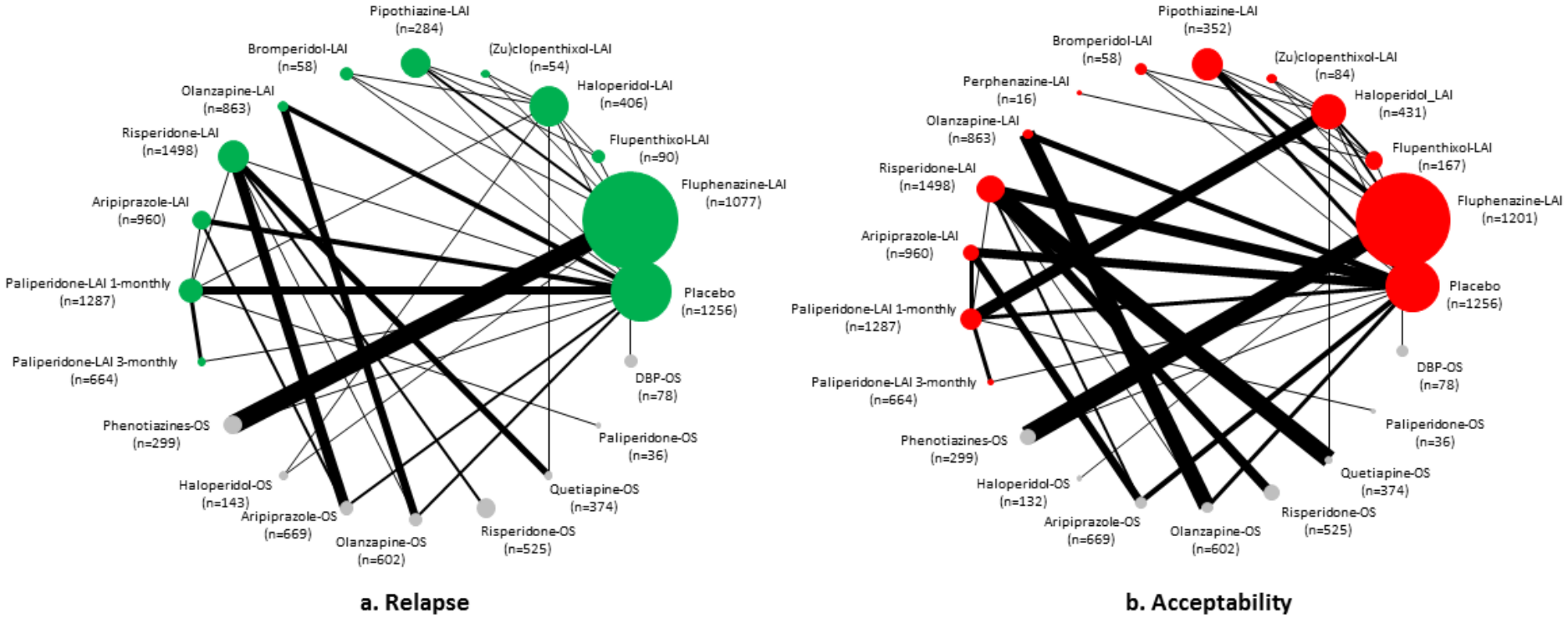


Figure 3. Network plots of evidence for relapse (left) and acceptability (right). The thickness of lines is proportional to the precision of each direct estimate and the size of circles is proportional to the number of studies including that treatment. n=number of participants randomized to each treatment; LAI=long-acting antipsychotics; OS=oral antipsychotics; BDP=diphenylbutylpiperidine derivatives (pimozine, penfluridol); Phenothiazines=fluphenazine, trifluoperazine, chlorpromazine.

Aripiprazole LAI	**2.10 (1.03 to 4.28)**	1.27 (0.86 to 1.88)	**1.37 (1.06 to 1.76)**	1.30 (0.99 to 1.71)	1.26 (0.93 to 1.71)	**1.43 (1.14 to 1.79)**	1.23 (0.87 to 1.75)	0.64 (0.06 to 6.58)	**1.50 (1.09 to 2.05)**	**1.42 (1.11 to 1.82)**	0.68 (0.27 to 1.73)	**2.05 (1.71 to 2.44)**
0.57 (0.24 to 1.39)	**Bromperidol LAI**	0.61 (0.29 to 1.28)	0.65 (0.33 to 1.29)	0.62 (0.31 to 1.24)	0.60 (0.29 to 1.25)	0.68 (0.34 to 1.37)	0.58 (0.28 to 1.24)	0.30 (0.03 to 3.41)	0.71 (0.35 to 1.46)	0.68 (0.33 to 1.38)	0.32 (0.10 to 1.00)	0.97 (0.49 to 1.94)
0.90 (0.41 to 1.95)	1.57 (0.58 to 4.25)	**Flupenthixol LAI**	1.07 (0.76 to 1.52)	1.02 (0.75 to 1.39)	0.99 (0.64 to 1.53)	1.12 (0.78 to 1.61)	0.97 (0.62 to 1.51)	0.50 (0.05 to 5.01)	1.18 (0.80 to 1.73)	1.12 (0.76 to 1.65)	0.54 (0.22 to 1.32)	**1.61 (1.12 to 2.30)**
0.83 (0.53 to 1.31)	1.45 (0.67 to 3.14)	0.93 (0.49 to 1.75)	**Fluphenazine LAI**	0.95 (0.75 to 1.21)	0.92 (0.67 to 1.26)	1.05 (0.82 to 1.34)	0.90 (0.63 to 1.29)	0.47 (0.05 to 4.79)	1.10 (0.86 to 1.40)	1.04 (0.80 to 1.35)	0.50 (0.20 to 1.25)	**1.50 (1.23 to 1.82)**
0.51 (0.28 to 0.93)	0.88 (0.37 to 2.12)	0.56 (0.26 to 1.20)	**0.61 (0.37 to 0.99)**	**Haloperidol LAI**	0.97 (0.69 to 1.36)	1.10 (0.89 to 1.36)	0.94 (0.67 to 1.33)	0.49 (0.05 to 4.99)	1.15 (0.85 to 1.56)	1.09 (0.83 to 1.44)	0.52 (0.21 to 1.29)	**1.57 (1.24 to 1.99)**
0.77 (0.49 to 1.22)	1.34 (0.54 to 3.32)	0.86 (0.39 to 1.90)	0.92 (0.57 to 1.51)	1.53 (0.80 to 2.89)	**Olanzapine LAI**	1.13 (0.83 to 1.55)	0.98 (0.65 to 1.47)	0.50 (0.05 to 5.26)	1.19 (0.83 to 1.71)	1.13 (0.83 to 1.53)	0.54 (0.21 to 1.40)	**1.62 (1.27 to 2.07)**
0.74 (0.51 to 1.08)	1.29 (0.54 to 3.07)	0.82 (0.39 to 1.75)	0.89 (0.58 to 1.36)	1.46 (0.81 to 2.64)	0.96 (0.62 to 1.48)	**Paliperidone LAI 1-monthly**	0.86 (0.64 to 1.15)	0.45 (0.04 to 4.58)	1.05 (0.77 to 1.43)	0.99 (0.76 to 1.30)	0.48 (0.19 to 1.20)	**1.43 (1.18 to 1.74)**
1.07 (0.63 to 1.81)	1.86 (0.71 to 4.83)	1.18 (0.51 to 2.77)	1.28 (0.73 to 2.25)	**2.11 (1.05 to 4.24)**	1.38 (0.79 to 2.43)	1.44 (0.95 to 2.19)	**Paliperidone LAI 3-monthly**	0.52 (0.05 to 5.41)	1.22 (0.81 to 1.83)	1.16 (0.80 to 1.68)	0.55 (0.21 to 1.44)	**1.66 (1.20 to 2.31)**
-	-	-	-	-	-	-	-	**Perphenazine LAI**	2.35 (0.23 to 24.33)	2.23 (0.22 to 23.10)	1.07 (0.09 to 12.70)	3.21 (0.31 to 33.07)
0.82 (0.43 to 1.55)	1.42 (0.57 to 3.57)	0.91 (0.41 to 2.03)	0.98 (0.59 to 1.63)	1.62 (0.82 to 3.19)	1.06 (0.54 to 2.06)	1.10 (0.59 to 2.05)	0.77 (0.37 to 1.58)	-	**Pipothiazine LAI**	0.95 (0.69 to 1.31)	0.45 (0.18 to 1.16)	**1.36 (1.05 to 1.78)**
0.83 (0.54 to 1.27)	1.44 (0.58 to 3.61)	0.92 (0.41 to 2.07)	0.99 (0.59 to 1.67)	1.64 (0.87 to 3.10)	1.08 (0.63 to 1.83)	1.12 (0.70 to 1.79)	0.78 (0.42 to 1.43)	-	1.02 (0.51 to 2.01)	**Risperidone LAI**	0.48 (0.19 to 1.22)	**1.44 (1.18 to 1.75)**
0.69 (0.21 to 2.28)	1.21 (0.31 to 4.65)	0.77 (0.22 to 2.76)	0.83 (0.27 to 2.56)	1.37 (0.46 to 4.14)	0.90 (0.27 to 3.01)	0.94 (0.29 to 3.05)	0.65 (0.19 to 2.24)	-	0.85 (0.25 to 2.89)	0.84 (0.25 to 2.80)	**(Zu)clopenthixol LAI**	**3.00 (1.20 to 7.53)**
0.29 (0.21 to 0.39)	0.50 (0.22 to 1.15)	**0.32 (0.16 to 0.65)**	**0.34 (0.24 to 0.48)**	**0.57 (0.33 to 0.97)**	**0.37 (0.26 to 0.53)**	**0.39 (0.30 to 0.50)**	**0.27 (0.17 to 0.42)**	-	**0.35 (0.20 to 0.62)**	**0.34 (0.23 to 0.52)**	0.41 (0.13 to 1.31)	**Placebo**

Relapse Acceptability

Table 3. Net league table: head-to-head comparisons for relapse (lower left part of the table) and acceptability (upper right part of the table). Relative risks and 95% confidence intervals are reported. For both relapse and acceptability, relative risks lower than 1 favor the column-defining treatment. Treatments are ordered alphabetically. Statistically significant results are in bold and underscored. LAI=long-acting antipsychotics

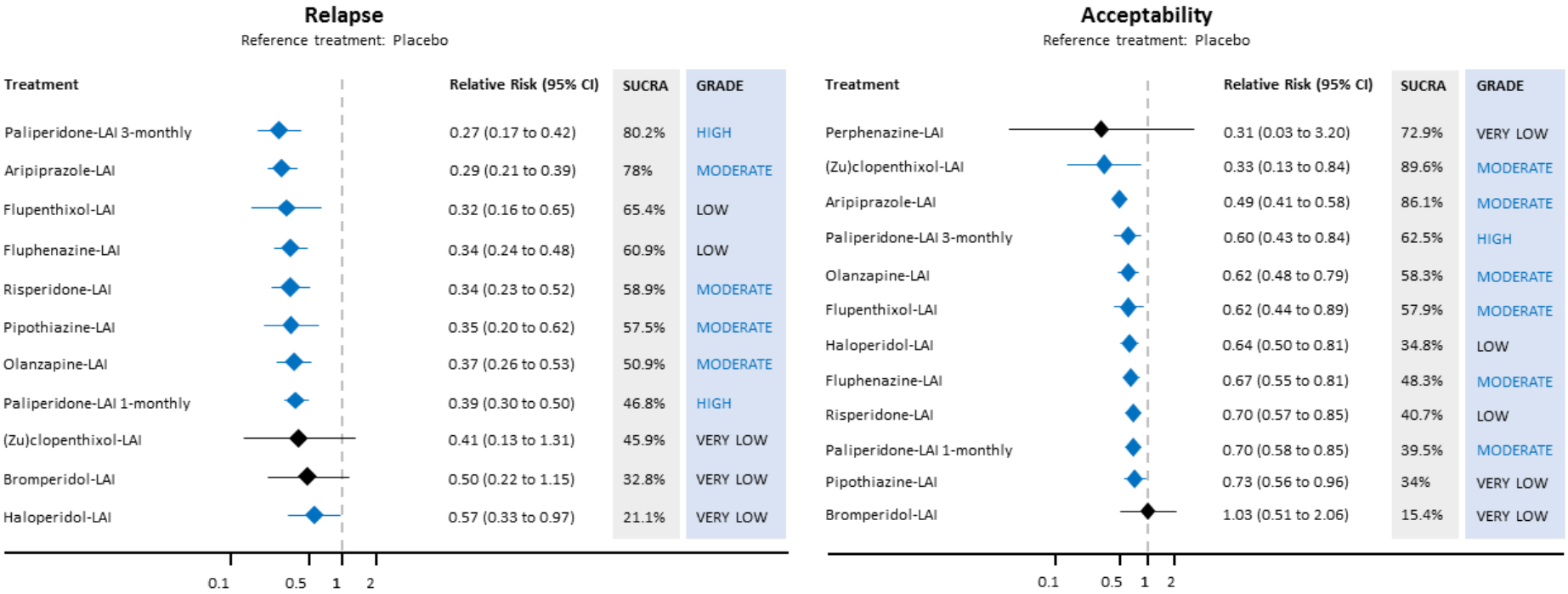


Figure 4. Forest plots comparing each LAI with placebo for relapse and acceptability to with the corresponding ranking probability (SUCRA) and certainty of evidence (GRADE), as assessed with the CINeMA appraisal, for each intervention. Statistically significant results are colored in grey. CI=confidence interval; LAI=long-acting antipsychotics; SUCRA=surface under the cumulative ranking; GRADE=Grading of Recommendations Assessment Development and Evaluation.

Secondary outcomes included:

- **Efficacy measured as mean change score:** the following LAIs (ordered from the largest to the smallest point estimate) were significantly superior than placebo: perphenazine-LAI, pipothiazine-LAI, risperidone-LAI, aripiprazole-LAI, haloperidol-LAI, fluphenazine-LAI and paliperidone-LAI 1-monthly. No significant differences emerged from head-to-head comparisons. Significant overall heterogeneity and incoherence emerged, related to relevant heterogeneity in some pairwise comparisons and intra-loop incoherence, involving mostly placebo, haloperidol-LAI, aripiprazole-LAI and fluphenazine-LAI. There was statistical agreement between direct and indirect estimates;
- **Quality of life:** data were available for three LAIs only (aripiprazole-LAI, risperidone-LAI and paliperidone-LAI 1-monthly) and placebo was not included. The network had no triangular or quadratic loops. In head-to-head comparisons, aripiprazole-LAI was superior to paliperidone-LAI 1-monthly. Significant overall heterogeneity and incoherence emerged for this network, related to the very high heterogeneity of the comparison aripiprazole-LAI versus paliperidone-LAI 1-monthly. There was statistical agreement between direct and indirect estimates;
- **Hospitalization:** significantly lower hospitalization rates for aripiprazole-LAI, paliperidone-LAI 3-monthly, haloperidol-LAI, fluphenazine-LAI and paliperidone-LAI 1-monthly versus placebo (LAIs ordered from the largest to the smallest point estimate);
- **Functioning:** a network meta-analysis could not be carried out. Pairwise meta-analyses were performed, but no significant differences between treatments emerged, except for paliperidone-LAI 3-monthly showing better functioning than placebo based on results from one study only.

Although also paliperidone palmitate 3-month long-acting injection showed to be effective and acceptable, and had the largest point estimate in terms of relapse prevention, we decided to not consider this medication for the present proposal, for the following reasons:

a. Paliperidone palmitate 3-month long-acting has been available only in relatively recent times (approved by EMA in 2016 and subsequently marketed)[9], therefore it is still not commonly used in clinical practice, and there might be problems of availability worldwide;
b. Some concerns had been raised around the randomized study comparing paliperidone palmitate 3-month long-acting and placebo (53). In this study, participants underwent a stabilization phase with paliperidone-LAI 1-monthly before randomization to the 3-monthly formulation or placebo. This study design might have inflated the effect size of paliperidone-LAI 3-monthly by using a particularly enriched sample for benefit and tolerability in persons ultimately randomized to the placebo discontinuation phase of the study. For this reason, results should be interpreted carefully;

[9] https://www.ema.europa.eu/en/documents/overview/trevicta-previously-paliperidone-janssen-epar-summary-public_en.pdf

c. More research is needed to rule out possible unintended consequences of this formulation of paliperidone. For example, a 3-month dosing interval may induce doctors to visit their patients less frequently, and this may in turn negatively affect the therapeutic relationship, the early recognition of a worsening in symptomatology, and the regular monitoring of safety parameters. Paradoxically, therefore, a longer dosing interval intended to increase adherence might actually lower adherence to treatment as a whole, especially in the long-term. Moreover, as the cumulative monthly dose of PP3M is slightly higher than that of PP1M, it is possible that in the long-term this increased amount of antipsychotic may be associated with consequences in terms of toxicity and tolerability (52).

In synthesis, **current scientific evidence on the comparison between oral and long-acting antipsychotics showed the two formulations to be at least equally effective, tolerable and safe**. When compared long-acting antipsychotics head-to-head in a network meta-analysis, risperidone long-acting and paliperidone palmitate 1-month long-acting injection showed to be:

a. superior to placebo in reducing the risk of relapse, with effect sizes similar to those of other long-acting antipsychotics included in the analysis, and "moderate" (risperidone long-acting) and "high" (paliperidone long-acting) certainty of evidence according to the GRADE approach. No statistically significant differences emerged when compared head-to-head to other long-acting antipsychotics;
b. more acceptable than placebo in terms of overall dropouts (to be considered as a pragmatic measure of the balance between efficacy and tolerability), with effect sizes similar to those of other long-acting antipsychotics included in the analysis, and "low" (risperidone long-acting) and "moderate" (paliperidone long-acting) evidence according to the GRADE approach. No statistically significant differences emerged when compared head-to-head to other long-acting antipsychotics, with the exception of aripiprazole-LAI, which showed a better acceptability profile as compared to both these medications.

Results from this network meta-analysis expand findings from previous studies, including data from large observational studies. According to a large Swedish database study (48), in which 29 823 adults with a diagnosis of schizophrenia ("prevalent population") were followed between 2006 and 2013, both risperidone long-acting and paliperidone palmitate 1-month long-acting appeared effective in preventing psychiatric re-hospitalization as compared to both no use of antipsychotics (paliperidone long-acting: hazard ratio (HR) 0.51; 95% CI 0.41 to 0.64; risperidone long-acting: HR 0.61; 95% CI 0.55 to 0.68) and oral olanzapine (paliperidone long-acting: HR 0.72; 95% CI 0.62 to 0.83; risperidone long-acting: HR 0.80; 95% CI 0.73 to 0.87) with an effect size comparable to those of other long-acting antipsychotics (Figure 4).

(A) Psychiatric rehospitalization during monotherapy compared with no use of antipsychotics

Treatment	HR (95% CI)
LAI paliperidone	0.51 (0.41-0.64)
LAI zuclopenthixol	0.53 (0.48-0.57)
Oral clozapine	0.53 (0.48-0.58)
LAI perphenazine	0.58 (0.52-0.65)
LAI olanzapine	0.58 (0.44-0.77)
LAI risperidone	0.61 (0.55-0.68)
Polytherapy	0.62 (0.58-0.65)
Oral olanzapine	0.63 (0.59-0.68)
LAI haloperidol	0.64 (0.56-0.73)
Oral zuclopenthixol	0.67 (0.59-0.76)
Oral risperidone	0.71 (0.64-0.78)
Oral aripiprazole	0.73 (0.66-0.81)
Oral levomepromazine	0.76 (0.66-0.89)
LAI flupentixol	0.78 (0.62-0.98)
Oral haloperidol	0.81 (0.71-0.93)
LAI fluphenazine	0.86 (0.35-2.08)
Other oral formulations	0.86 (0.75-0.98)
Oral perphenazine	0.86 (0.77-0.97)
Oral quetiapine	0.91 (0.83-1.00)
Oral flupentixol	0.92 (0.74-1.14)

(B) Psychiatric rehospitalization during each monotherapy compared with oral olanzapine

Treatment	HR (95% CI)
Oral clozapine	0.58 (0.53-0.63)
Polytherapy	0.61 (0.57-0.64)
LAI perphenazine	0.65 (0.59-0.71)
LAI haloperidol	0.67 (0.59-0.75)
LAI zuclopenthixol	0.69 (0.64-0.75)
LAI paliperidone	0.72 (0.62-0.83)
LAI flupentixol	0.75 (0.64-0.87)
LAI olanzapine	0.77 (0.60-0.98)
LAI fluphenazine	0.78 (0.45-1.35)
LAI risperidone	0.80 (0.73-0.87)
Oral perphenazine	0.93 (0.84-1.03)
Oral zuclopenthixol	0.95 (0.85-1.06)
Oral haloperidol	0.96 (0.86-1.06)
Oral flupentixol	1.03 (0.90-1.18)
Oral quetiapine	1.05 (0.97-1.13)
Oral risperidone	1.05 (0.97-1.13)
Other oral formulations	1.12 (1.02-1.22)
Oral aripiprazole	1.12 (1.04-1.21)
Oral levomepromazine	1.15 (1.02-1.28)

Figure 4. Adjusted hazard ratios (HRs) and 95% confidence intervals psychiatric rehospitalization during monotherapy compared with no use of antipsychotics (A) and during each monotherapy compared with oral olanzapine (B). Data from Tiihonen et al., JAMA Psychiatry 2017

Although the comparability between oral and long-acting antipsychotics is debated, two systematic reviews and meta-analyses of randomized trials failed to detect significant differences between those two formulations in terms of efficacy, overall acceptability, tolerability and common adverse events (36, 47). On these premises, it is relevant to acknowledge that, according to the network meta-analysis by Huhn and colleagues (1), which included randomized trials of adults with multi-episode schizophrenia and treated with oral antipsychotics for acute symptoms, both oral risperidone and paliperidone were among the best performing medications as compared to placebo in reducing overall discontinuation (GRADE certainty: high for both), overall psychotic symptoms (GRADE certainty: high for both), positive symptoms (GRADE certainty: moderate for both), negative symptoms (GRADE certainty: moderate for both). In terms of head-to-head comparisons, risperidone was more effective than ziprasidone, more acceptable than ziprasidone and haloperidol and less acceptable that olanzapine, and paliperidone was more acceptable than ziprasidone and haloperidol. No other relevant differences of both efficacy and acceptability emerged as compared to other oral antipsychotics for which a long-acting formulation is available. These data confirm the efficacy of risperidone and paliperidone, although they should be cautiously interpreted due to the risk of indirectness,

as these randomized trials were performed in acutely ill people, while randomized trials on long-acting antipsychotics included stable people requiring maintenance treatment.

10. Review of harms and toxicity: summary of evidence of safety.

The systematic review and network meta-analysis conducted to inform this application considered the following side effects of LAIs:

- **Dropouts due to adverse events ("tolerability")**: paliperidone-LAI 1-monthly was less tolerable than placebo, while for other LAIs no differences versus placebo emerged. Aripiprazole-LAI was more tolerable than paliperidone-LAI 1-monthly, while no other significant differences emerged in head-to-head comparisons;
- **Weight gain**: significantly higher weight gain emerged for paliperidone-LAI 1-monthly, paliperidone-LAI 3-monthly and aripiprazole-LAI versus placebo;
- **Hyperprolactinaemia**: significantly higher risk of hyperprolactinaemia for paliperidone-LAI 1-monthly, paliperidone-LAI 3-monthly and olanzapine-LAI versus placebo;
- **Extrapyramidal symptoms**: no LAIs showed a significantly higher risk of extrapyramidal symptoms versus placebo;
- **QTc prolongation and sedation**: the network meta-analysis could not be performed. According to pairwise meta-analyses, no significant differences between treatments emerged, except for paliperidone-LAI 3-monthly showing lower risk of QTc prolongation than paliperidone-LAI 1-monthly, based on results from one study only.

Considering the relative paucity of data on specific side-effects, mostly due to reporting bias of original studies, other systematic reviews might provide useful information:

- As described above, previous systematic reviews and meta-analyses (36, 47) failed to show relevant differences between the oral and LAI formulation of the same antipsychotic medication. Based on this principle, we can reasonably expect that the tolerability profile described by the most updated systematic reviews on oral antipsychotic can be extended to long-acting antipsychotics. The network meta-analysis by Huhn and colleagues (1) showed both oral risperidone and paliperidone to be worse than placebo in terms of weight gain (risperidone: mean difference (MD) (kg) 1.44; 95% CI 1.05 to 1.83; 2521 participants; GRADE certainty: high; paliperidone: MD (kg) 1.49; 95% CI 0.98 to 2.00; 1536 people; GRADE certainty: high), use of antiparkinson medications (risperidone: RR 1.80; 95% CI 1.40 to 2.38; 2174 participants; GRADE certainty: low; paliperidone: RR 1.61; 95% CI 1.17 to 2.10; 1355 participants; GRADE certainty: very low) and prolactin increase (risperidone: MD (ng/mL) 37.98; 95% CI 34.64 to 41.38; 1761

participants; GRADE certainty: moderate; paliperidone: MD (ng/mL) 48.51; 95% CI 43.52 to 53.51; 1067 participants; GRADE certainty: moderate);

- The systematic review and meta-analysis by Kishi and colleagues (46) assessed the risk of death associated with long-acting and oral antipsychotics in people with schizophrenia. 52 randomized controlled trials were included, comprising 17,416 participants. Neither pooled nor individual long-acting antipsychotics (aripiprazole, fluphenazine, olanzapine, paliperidone, and risperidone) differed from placebo regarding the incidences of all-cause death (overall RR 0.64; 95% CI 0.24 to 1.70; I^2=0%; 18 studies; 5919 participants). Similarly, pooled long-acting antipsychotics (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) did not differ from pooled oral antipsychotics regarding all-cause death (overall RR 0.71; 95% CI 0.38 to 1.34; I^2=0%; 24 studies; 7879 participants). Secondary analyses showed no differences between long-acting and both placebo and oral antipsychotics in terms of suicide. Individual long-acting antipsychotics and oral antipsychotics showed similar risks of death. Data for head-to-head comparisons between individual long-acting antipsychotics were insufficient to draw any conclusion.

Additional information can be derived from the Summary of Product Characteristics, Labelling and Package Leaflet, released by the EMA. Excerpts from the "Annex III" of both risperidone long-acting paliperidone palmitate 1-month long-acting are reported in the Appendix.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Table 4 provide some examples of the net costs of the most commonly used long-acting antipsychotics in different contexts, as reported by national formularies. 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. Despite that, long-acting might be theoretically cost-effective by reducing hospitalizations and therefore lowering inpatient spending. 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.

A recent 1-year mirror-image study conducted in North Staffordshire (UK), including 30 people receiving aripiprazole long-acting and 84 receiving paliperidone palmitate 1-month long-acting, showed a significant reduction in both bed occupancy and hospital admission as compared to the period preceding the introduction of the long-acting, with estimated minimum savings of £14,175 (aripiprazole) and £13,750 (paliperidone) (49). Similarly, a mirror-image study conducted in Spain, including 71 outpatients initiating paliperidone palmitate 1-month long-acting, showed a reduction of hospitalizations, shortening in hospitalization days, abridgement of number of emergency assists, and decreased rate of antipsychotics

associated to long-acting treatment, leading to an overall reduction in inpatient spending (savings of €175,766.54) and increased spending in terms of antipsychotic costs of 32% (equivalent to €151,126.92) (50). The pragmatic randomized trial ACLAIMS (A Comparison of Long-acting Injectable Medications for Schizophrenia) included 311 participants, who were allocated to haloperidol decanoate and paliperidone palmitate. The latter showed a better efficacy profile in terms of QALYs (0.027 greater QALYs over 18 months), but also greater average quarterly inpatient, outpatient and medication costs. The cost-effectiveness analysis showed Incremental Cost effectiveness ratio for paliperidone palmitate of $508,241/QALY (95% CI of $122,390 to $1,582,711), and the Net Health Benefits analysis showed a 0.98 probability of greater cost-effectiveness for haloperidol decanoate over paliperidone palmitate at an estimated valuation of health of $150,000/QALY and only 0.50 greater at $500,000/QALY. Authors concluded that, as haloperidol decanoate was overall more cost-effective than paliperidone palmitate, the markedly higher on-patent costs of the latter is not justified by its slightly greater benefits (51).

Table 4. Net costs of the most commonly used long-acting antipsychotics in different countries, expressed in dollars (currency converter: xe.com).

	Italy	U.K.	U.S.	Brazil	India	South Africa
Risperidone long-acting	**RISPERDAL CONSTA (Janssen-Cilag)** 25mg = 185 $ 37,5mg = 240 $ 50mg = 300 $	**RISPERDAL CONSTA (Janssen-Cilag)** 25mg = 105 $ 50mg = 146 $ 75mg = 188 $	**RISPERDAL CONSTA (Janssen-Cilag)** 12.5mg = 275 $ 25mg = 540 $ 37,5mg = 805 $ 50mg = 1071 $	**RISPERDAL CONSTA (Janssen-Cilag)** 37,5mg = 222 $ 50mg = 320 $	**RISPERDAL CONSTA (Janssen-Cilag)** 50mg = 121 $	**RISPERDAL CONSTA (Janssen-Cilag)** 25mg = 121$ 37,5mg = 164 $ 50mg = 207 $
Paliperidone palmitate 1-month long-acting	**XEPLION (Janssen-Cilag)** 50mg = 398 $ 75mg = 514 $ 100mg = 655 $ 150mg = 804 $	**XEPLION (Janssen-Cilag)** 50mg = 242 $ 75mg = 323 $ 100mg = 414 $ 150mg = 517 $	**INVEGA SUSTENNA (Janssen-Cilag)** 50mg = 985 $ 75mg = 1474 $ 100mg = 1962 $ 150mg = 2938 $	**INVEGA (Janssen-Cilag)** 100mg = 326 $	**INVEGA SUSTENNA (Janssen-Cilag)** 75mg = 121 $ 100mg = 121 $ 150mg = 121 $	**XEPLION (Janssen-Cilag)** 50mg = 193 $ 75mg = 281 $ 100mg = 370 $ 150mg = 547 $
Paliperidone palmitate 3-months long-acting	**TREVICTA (Janssen-Cilag)** 175mg = 1197 $ 263mg = 1545 $ 350mg = 1930 $ 525mg = 3105 $	**TREVICTA (Janssen-Cilag)** 175mg = 728 $ 263mg = 969 $ 350mg = 1242 $ 525mg = 1553 $	**TRINZIGA (Janssen-Cilag)** 273mg = 2938 $ 410mg = 4402 $ 546mg = 5867 $ 819mg = 8796 $	**NA**	**NA**	**NA**
Olanzapine pamoate long-acting	**ZYPADHERA (Eli Lilly and Company Ltd)** 210mg = 288 $ 300mg = 450 $ 405mg = 578 $	**ZYPADHERA (Eli Lilly and Company Ltd)** 210mg = 188 $ 300mg = 294 $ 405mg = 377 $	**ZYPREXA RELPREVV (Eli Lilly and Company Ltd)** 210mg = 625 $ 300mg = 889 $ 405mg = 1197 $	**NA**	**NA**	**NA**

Aripiprazole long-acting	**ABILIFY MAINTENA (Otsuka Pharmaceuticals (U.K.) Ltd)** 400mg = 520 $	**ABILIFY MAINTENA (Otsuka Pharmaceuticals (U.K.) Ltd)** 400mg = 290 $	**ABILIFY MAINTENA (Otsuka Pharmaceuticals (U.K.) Ltd)** 300mg = 1790 $ 400mg = 2384 $	**NA**	**NA**	**NA**
Fluphenazine enantate/decanoate long-acting	**MODITEN (Sanofi)** 25mg = 5,3 $	**MODECATE (Sanofi)** 25mg = 30 $ 100mg = 58 $	**FLUPHENAZINE DECANOATE (various companies)** 25mg = 75 $	**FLUFENAN DEPOT (Cristalia Ltda)** 25mg = 34 $	**ANATENSOL DECANOATE (Nicholas Piramal India Ltd)** 25mg = 0.68 $	**MODECATE (Bristol Meyer Squibb)** 25mg = 19 $
Haloperidol decanoate long-acting	**HALDOL DECANOAS (Janssen-Cilag Ltd)** 50mg = 11,3 $	**HALDOL DECANOATE (Janssen-Cilag Ltd)** 50mg = 25 $ 100mg = 33 $	**HALDOL DECANOATE (Teva)** 50mg = 33 $ 100mg = 40 $	**DECANOATO DE HALOPERIDOL (Cristalia Ltda))** 50mg = 3,6 $	**SERENACE DEPOT (various companies)** 50mg = 0.08 $	**NA**
Zuclopenthixol decanoate long-acting	**CLOPIXOL (Lundbeck Ltd)** 200mg = 7 $	**CLOPIXOL (Lundbeck Ltd)** 200mg = 42 $ 500mg = 49 $	**NA**	**CLOPIXOL (Lundbeck Ltd)** 200mg = 13 $	**CLOPIXOL (Lundbeck Ltd)** 200mg = 8 $	**CLOPIXOL (Lundbeck Ltd)** 200mg = 12 $

Legend: mg=milligrams; NA=not available

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

Risperidone long-acting has been approved under the trade name of Risperdal® Consta® by the FDA for (a) the treatment of schizophrenia, and (b) as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder; and by the EMA for the maintenance treatment of schizophrenia in people currently stabilized with oral antipsychotics.

Paliperidone long-acting has been approved under the trade name of Invega® Sustenna® by the FDA for (a) the treatment of schizophrenia, and (b) the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants; and by the EMA under the trade name of Xeplion® for the maintenance treatment of schizophrenia in adults whose disease has already been stabilized on treatment with paliperidone or risperidone.

None of these medications has been approved for use in children and adolescents.

The availability of long-acting medications may notably vary between countries. According to the manufacturer the two medicines are marketed in the following countries[10]:

- Risperidone long-acting: Argentina; Australia; Austria; Belgium; Brazil; Canada; Chile; China; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Japan; Korea; Latvia; Lithuania; Netherlands; New Zealand; Norway; Poland; Portugal; Romania; Russia; Uruguay; United States; United Kingdom; Spain; Sweden; Slovenia; Slovakia; Switzerland;
- Paliperidone palmitate 1-month long-acting: Argentina; Australia; Austria; Belgium; Brazil; Canada; Chile; China; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Japan; Korea; Latvia; Lithuania; Netherlands; New Zealand; Norway; Poland; Portugal; Romania; Russia; United States; United Kingdom; Spain; Sweden; Slovenia; Slovakia; Switzerland.

Patent status

Various types of patent may be granted for pharmaceuticals. In general, besides "primary" patents covering the specific active molecule (a "product patent" or "compound patent"), there are "secondary" patents, covering aspects such as method of use, specific formulations (e.g. formulation as a tablet with specific excipients), treatment regimens or production methods. In general, it is safe to assume that an unexpired "product patent", where it is granted and in force, will block prevent generic products from entering the market. On the other hand, whether "secondary patents" can block generic market entry is a more controversial issue. For the purposes of this application, the main patents and patent applications relating to

[10] Source: https://www.janssen.com/products/Neuroscience

the products of interest were identified through the US FDA Orange Book[11] and Health Canada Patent Register databases[12]. Both regulatory agencies list patents relevant to approved medicines that are provided by market authorization holders. The Canadian and/or US patents retrieved are used to identify equivalent patents/patent applications in other jurisdictions using regional or national patent office public databases. In general, it is safe to assume that, if there are no "unexpired" patents left in Canada and US for a certain product, it is unlikely there will be in other countries.

It should however be noted that the patent information provided herein may not be comprehensive and further analysis might be required to identify patents directed to categories excluded from the US FDA Orange Book or Health Canada Patent Register (e.g. manufacturing processes) or patent applications that have not yet been made public.

The dedicated search with these repositories provided the following information:

Risperidone long-acting was approved by the FDA on October 29th, 2003 (trade name of Risperdal® Consta®; Application n. 021346; Company: Johnson & Johnson Pharmaceutical Research) and by the EMA on October 7th, 2008 (trade name: Risperdal® Consta®; Reference n. CHMP/384879/08; Marketing-authorisation holder: Janssen-Cilag). As shown in Table 5, risperidone long-acting compound patents expired between 2006-2007 worldwide. Two patent families on microparticles listed in the Health Canada Patent Register database expired between 2014 and 2019. The last patent family listed in the table below covering an improved formulation is expected to expire early 2021. The patents on the formulations are owned or co-owned by Alkermes.

[11] https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
[12] https://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp

Table 5. Primary and secondary patents for risperidone long-acting and their expected expiry date

Patent Description	Representative patent publication	Expected date of expiry	Source	Comments/countries
1,2-Benzisoxazol-3-yl and 1,2-benzisothiazol-3-yl derivatives.	EP0196132 (national filings) - Janssen	13/03/2006	Merck Index	Compound - EXPIRED
MICROENCAPSULATED 3-PIPERIDINYL-SUBSTITUTED 1,2-BENZISOXAZOLES AND 1,2-BENZISOTHIAZOLES	WO1995013814 (Janssen & Alkermes)[13]	11/11/2014	CA2175370 2014/11/11	Formulation - EXPIRED
PREPARATION OF MICROPARTICLES HAVING A SELECTED RELEASE PROFILE	WO2000040221 (Alkermes)[14]	10/12/2019	CA2352818 10/12/2019	Formulation - EXPIRED
PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY	WO0191720 (Alkermes)[15]	19/04/2021	CA2406536 US6667061	Formulation - UNEXPIRED Filed in: Australia, Brazil, Canada, China, Israel, Japan, Korea, Mexico, Norway, New Zealand, Singapore. Granted in: Canada, US, Europe (Austria, UK, Sweden, Spain, Denmark, Luxembourg, Cyprus, Netherlands, Monaco, Ireland, Portugal, France, Switzerland, Germany, Finland, France, Lithuania, North Macedonia.

Paliperidone palmitate 1-month long-acting was approved by the FDA on July 7th, 2009 (trade name: Invega® Sustenna®, Application n. 022264; Company: Ortho-McNeil-Janssen Pharmaceuticals, Inc.) and by the EMA on March 4th, 2011 (trade name: Xeplion®; Agency product n. EMEA/H/C/002105; Marketing-authorisation holder: Janssen-Cilag International N.V.). As shown in Table 6, the compound patents expired in 2009 whereas patents on aqueous suspensions comprising the compounds expired between 2017 and 2018. The only family currently listed in both the US orange book and Health Canada Patent Register database is a secondary patents covering the treatment regimen currently approved. Applications were filed in several low and middle-income countries, as well as high-income countries. Further consultation might be necessary to establish whether these patents represent a true block to generic market entry. This may indeed depend on the practical enforceability of method-of-use patents in each jurisdiction.

[13] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1995013814
[14] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2000040221
[15] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2001091720&_cid=P20-KHUMOR-91300-1

Table 6. Primary and secondary patents for paliperidone palmitate 1-month long-acting and their expected expiry date

Patent Description	Representative patent publication	Expected date of expiry	Source	Comments/countries
3-PIPERIDINYL-1,2-BENZISOXAZOLES	CA2000786 (national filings) - Janssen[16]	16/10/2009	CA2000786 16/10/2009	Compound - EXPIRED
AQUEOUS SUSPENSIONS OF 9-HYDROXYRISPERIDONE FATTY ACID ESTERS	WO9744039 (Janssen)[17]	12/05/2017	CA2236691 12/05/2017	Formulation - EXPIRED
AQUEOUS SUSPENSIONS OF SUBMICRON 9-HYDROXYRISPERIDONE FATTY ACID ESTERS	WO9925354 (Janssen)[18]	10/11/2018	CA2309629 10/11/2018	Formulation - EXPIRED
DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS	WO2009080651 (Janssen)[19]	17/12/2028	CA2655335 US9439906	Treatment Regimen - UNEXPIRED Filed in several LMICS and HICS. Granted in EA[20] (AM, AZ, BY, KZ, RU, MD), CA and US. Pending: EP[21], Indonesia, Mexico, Colombia, Nicaragua, Philippines (the list might not be exhaustive). Rejected or abandoned: India, Brazil and China (the list might not be exhaustive).

13. Availability of pharmacopoeial standards

Riperidone long-acting injection and paliperidone palmitate 1-month long-acting injection are included in the British Pharmacopoeia[22], United States Pharmacopoeia[23], European Pharmacopeia[24], while they are not included in the International Pharmacopoeia[25].

[16] https://worldwide.espacenet.com/publicationDetails/biblio?II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=19900507&CC=CA&NR=2000786A1&KC=A1

[17] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1997044039&tab=PCTBIBLIO&_cid=P20-KHUQDS-38126-1

[18] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1999025354&_cid=P20-KHUQEQ-38358-1

[19] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009080651&_cid=P20-KHUQFH-38636-1

[20] EA corresponds to regional patents granted by the Eurasian Patent Organization (EAPO)

[21] EP patents administered by the European Patent Organization. EP patents may cover most of European countries. In addition, European patents can for example be validated in Morocco if filed on or after 1 March 2015, in Tunisia if filed on or after 1 December 2017 and Cambodia if filed on or after 1 March 2018)

[22] https://www.pharmacopoeia.com/

[23] http://www.usp.org/

[24] http://online6.edqm.eu/ep907/

[25] https://apps.who.int/phint/en/p/about/

There are relevant differences between countries regarding the availability of antipsychotic drugs and their inclusion in the National Medicines List/Formulary/Standard Treatment Guidelines. For instance:

- **Afghanistan**: the "National Essential Drugs List, December 2007" includes oral and injectable chlorpromazine, oral and injectable haloperidol, oral fluphenazine and **long-acting fluphenazine decanoate**;
- **Brazil**: the "Relação Nacional de Medicamentos Essenciais 2010"[26] includes **haloperidol decanoate**, but not fluphenzine decanoate. Oral chlorpromazine, haloperidol and risperidone are included;
- **China**: the "Medicine List (for Primary Healthcare Facilities)(2009)"[27] includes oral and injectable perphenazine, chlorpromazine and haloperidol;
- **India**: the "National List of Essential Medicines of India 2011"[28] includes oral chlorpromazine and olanzapine, and injectable haloperidol. **No long-acting formulations are included**;
- **Nigeria**: the "Essential Medicines List, 5th Edition, Revision 2010"[29] includes oral and injectable chlorpromazine, oral haloperidol, and the **long-acting fluphenazine decanoate and haloperidol decanoate**;
- **South Africa**: the "Standard Treatment Guidelines and Essential Drugs List for South Africa - Hospital level - Adults (2006)"[30] includes oral and injectable haloperidol, oral chlorpromazine, risperidone, sulpride, clozapine, and **long-acting flupenthixol, fluphenazine and zuclopenthixol**;
- **Sweden**: the "Wise List 2015"[31] includes oral and **long-acting risperidone**, injectable zuclopenthixol, oral and **long-acting aripiprazole**; oral olanzapine and clozapine.

The "UNHCR Essential Medicines List" includes **fluphenazine enantate or decanoate, long-acting haloperidol decanoate**, oral and injectable haloperidol, oral risperidone. The "MSF Essential Drugs (July 2020)" includes oral chlorpromazine, haloperidol, risperidone, olanzapine, and promethazine; injectable chlorpromazine and haloperidol; **long-acting haloperidol decanoate and long-acting fluphenazine decanoate**[32].

[26] https://www.who.int/selection_medicines/country_lists/Brazil_rename2010.pdf?ua=1
[27] https://www.who.int/selection_medicines/country_lists/chn_eml_primarylevel_Western_medicines.pdf?ua=1
[28] https://www.who.int/selection_medicines/country_lists/India_NLME_2011.pdf?ua=1
[29] http://digicollection.org/hss/documents/s19018en/s19018en.pdf
[30] https://www.who.int/selection_medicines/country_lists/zaf_adult_2006.pdf?ua=1
[31] https://www.who.int/selection_medicines/country_lists/final_151028_the_wise_list_2015.pdf?ua=1
[32] https://medicalguidelines.msf.org/viewport/EssDr/english/essential-drugs-16682376.html

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APPENDICES

APPENDIX 1: Excerpts from EMA Annex III of risperidone long-acting and paliperidone palmitate 1-month long-acting

Paliperidone palmitate 1-month long-acting

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor immediately if you: · experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately. · have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke. · experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"). Immediate medical treatment may be needed. · are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed. · experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed. · experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an 'anaphylactic reaction'). Even if you have previously tolerated oral risperidone or oral paliperidone, rarely allergic reactions occur after receiving injections of paliperidone. · are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine. During an operation on the eye for cloudiness of the lens (cataract), the iris (the coloured part of the eye) may become floppy during surgery (known as "floppy iris syndrome") that may lead to eye damage. · are aware of having dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood.

The following side effects may happen:

Very common side effects: may affect more than 1 in 10 people · difficulty falling or staying asleep. Common side effects: may affect up to 1 in 10 people · common cold symptoms, urinary tract infection, feeling like you have the flu · Xeplion can raise your levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction; (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle. · high blood sugar, weight gain, weight loss, decreased appetite · irritability, depression, anxiety · parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face. · restlessness, feeling sleepy, or less alert · dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw. · dizziness · dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching. · tremor (shaking) · headache · rapid heart rate · high

blood pressure · cough, stuffy nose · abdominal pain, vomiting, nausea, constipation, diarrhoea, indigestion, toothache · increased liver transaminases in your blood · bone or muscle ache, back pain, joint pain · loss of menstrual periods · leakage of milk from the breasts · fever, weakness, fatigue (tiredness) · a reaction at the injection site, including itching, pain or swelling.

Uncommon side effects: may affect up to 1 in 100 people · pneumonia, infection of the chest (bronchitis), infection of the breathing passages, sinus infection, bladder infection, ear infection, fungal infection of the nails, tonsillitis · sleep walking · lack of emotion · inability to reach orgasm · neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness), blood vessel problems in the brain, including sudden loss of blood supply to brain (stroke or "mini" stroke), unresponsive to stimuli, loss of consciousness, low level of consciousness, convulsion (fits), balance disorder · abnormal coordination · glaucoma (increased pressure within the eyeball) · problems with movement of your eyes, eye rolling, oversensitivity of the eyes to light, increased tears, redness of the eyes · atrial fibrillation (an abnormal heart rhythm), irregular heart beat · blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg). If you notice any of these symptoms seek medical advice immediately · flushing · trouble breathing during sleep (sleep apnoea) · lung congestion · crackly lung sounds · inflammation of the pancreas, swollen tongue, stool incontinence, very hard stool · chapped lips · rash on skin related to drug, thickening of skin, dandruff · breakdown of muscle fibers and pain in muscles (rhabdomyolysis) · joint swelling · inability to pass urine · breast discomfort, enlargement of the glands in your breasts, breast enlargement · vaginal discharge · very low body temperature, chills, feeling thirsty · symptoms of drug withdrawal · accumulation of pus caused by infection at injection site, deep skin infection, a cyst at injection site, bruising at injection site.

Not known: frequency cannot be estimated from the available data · dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood · severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure · dangerously excessive intake of water · sleep-related eating disorder · coma due to uncontrolled diabetes · shaking of the head · blood clot in the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately. · decreased oxygen in parts of your body (because of decreased blood flow) · fast, shallow breathing, pneumonia caused by inhaling food, voice disorder · a blockage in the bowels, lack of bowel muscle movement that causes blockage · yellowing of the skin and the eyes (jaundice) · serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing · skin discolouration, flaky itchy scalp or skin · abnormal posture · newborn babies born to mothers who have taken Xeplion during pregnancy may experience side effects of the drug and/or withdrawal symptoms, such as irritability, slow, or sustained muscle contractions, shaking, sleepiness, breathing, or feeding problems · priapism (a prolonged penile erection that may require surgical treatment) · a decrease in body temperature · dead skin cells at the injection site and an ulcer at the injection site.

Risperidone long-acting

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

For risperidone-naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISPERDAL CONSTA (see section 4.2).

Elderly patients with dementia

RISPERDAL CONSTA has not been studied in elderly patients with dementia, hence it is not indicated for use in this group of patients.

Overall mortality

Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including oral RISPERDAL. In placebo-controlled trials with oral RISPERDAL in this population, the incidence of mortality was 4.0% for RISPERDAL-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).

Concomitant use with furosemide

In the oral RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular adverse events (CVAE)

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with RISPERDAL compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and

nonserious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RISPERDAL CONSTA should be used with caution in patients with risk factors for stroke.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during initiation of treatment. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease). The risk/benefit of further treatment with RISPERDAL CONSTA should be assessed if clinically relevant orthostatic hypotension persists.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including RISPERDAL CONSTA, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL CONSTA, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with RISPERDAL CONSTA. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Hyperprolactinaemia

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. RISPERDAL CONSTA should be used with caution in patients with preexisting hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

RISPERDAL CONSTA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism

Priapism may occur with RISPERDAL CONSTA treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RISPERDAL CONSTA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Weight gain

As with other antipsychotics, patients should be advised of the potential for weight gain. Weight should be measured regularly.

Renal or hepatic impairment

Although oral risperidone has been studied, RISPERDAL CONSTA has not been studied in patients with renal or liver insufficiency. RISPERDAL CONSTA should be administered with caution in this group of patients (see section 4.2).

Administration

Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA into a blood vessel.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially 'sodiumfree'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with oral RISPERDAL.

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressant (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Potential for RISPERDAL CONSTA to affect other medicinal products

Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

RISPERDAL CONSTA may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

RISPERDAL does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Potential for other medicinal products to affect RISPERDAL CONSTA

Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently, newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown. Therefore, RISPERDAL CONSTA should not be used during pregnancy unless clearly necessary.

Lactation

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse effects in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

APPENDIX 2: GRADE Tables

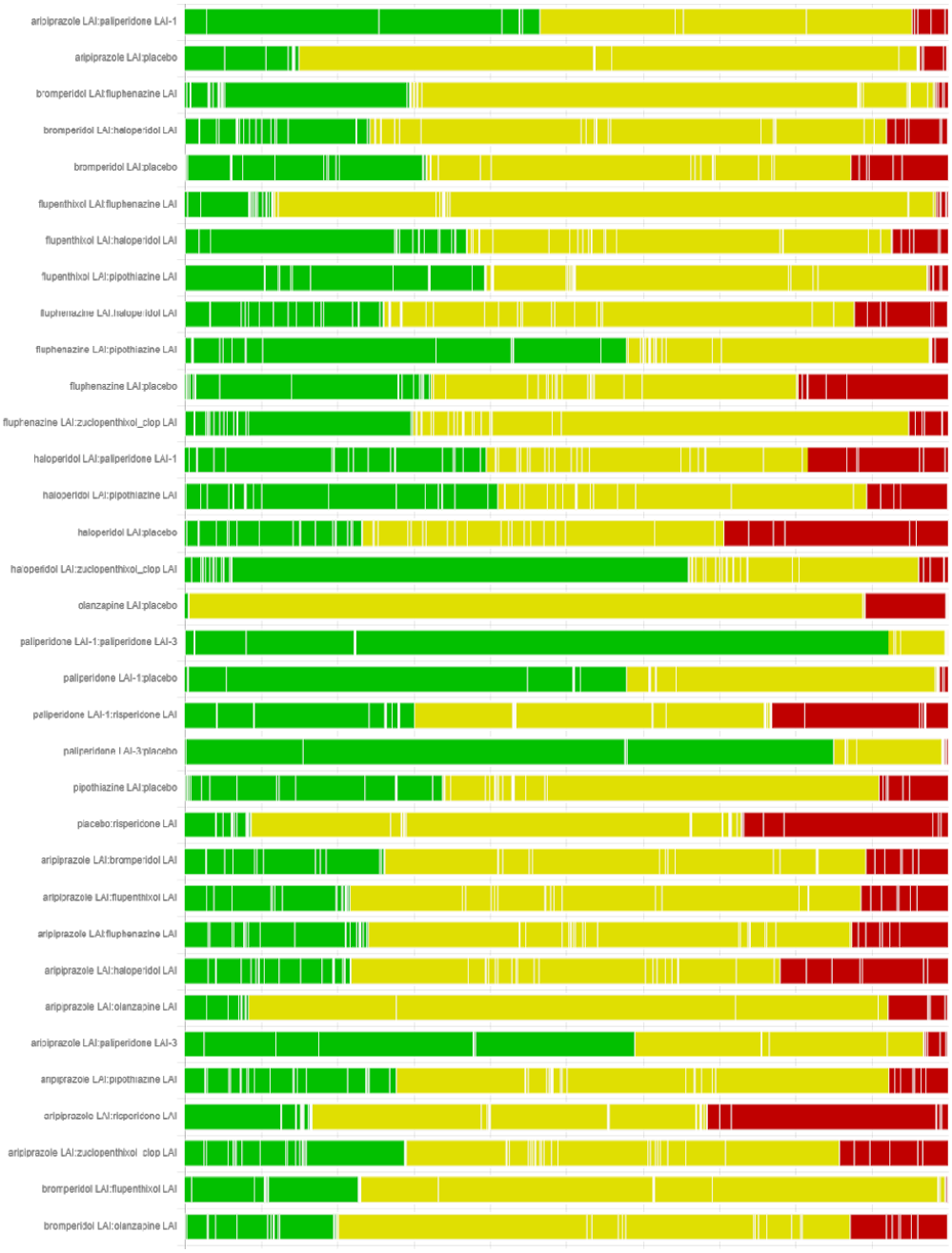
Outcome: relapse

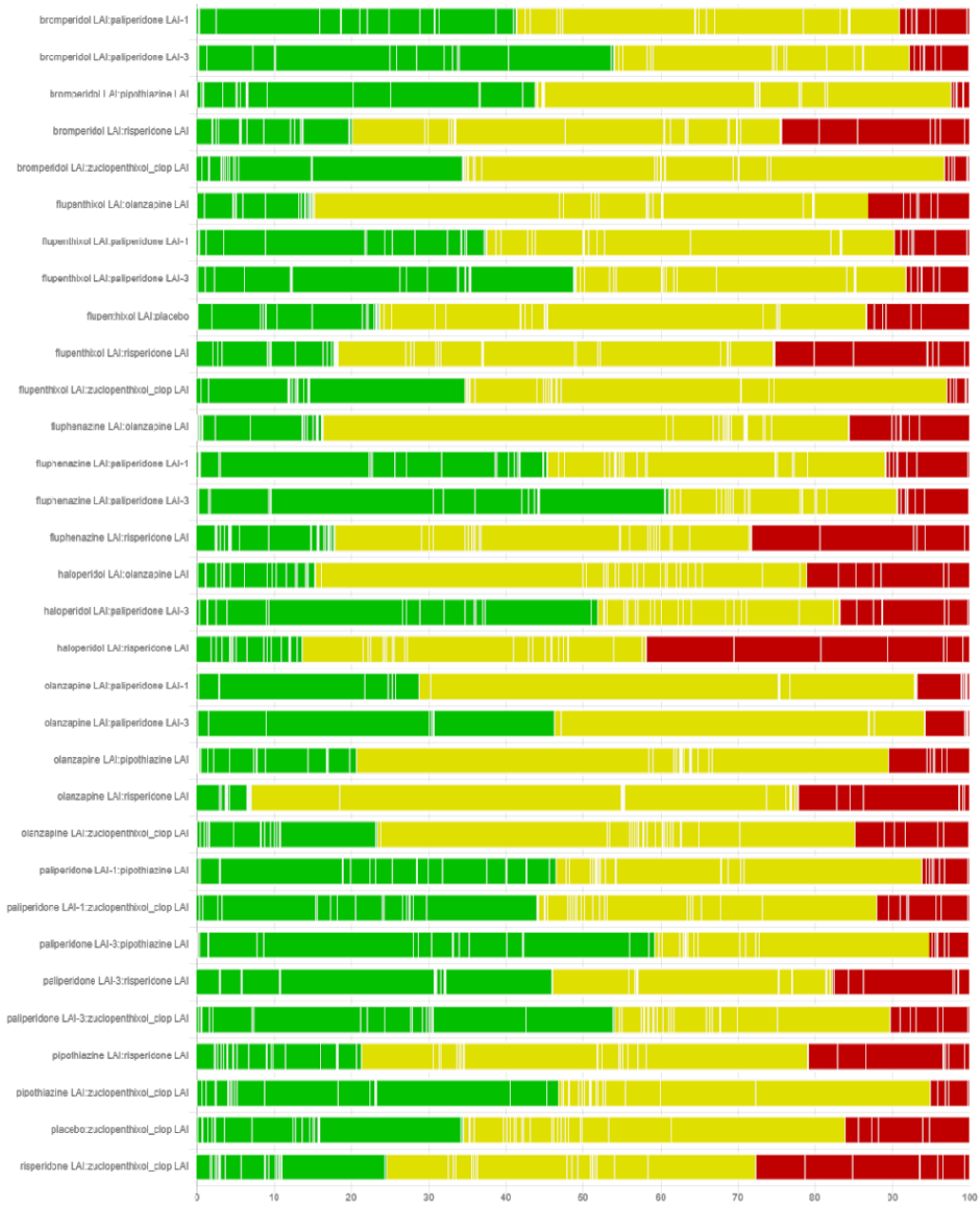
The analysis of the certainty of the evidence was performed with the online application CINeMA, which follows the principles of the GRADE methodology. The following criteria were applied:

- Within-study bias: the "overall" risk of bias of each study was calculated as follows: (a) LOW risk if four or more domains of the Cochrane RoB were at low risk (even if three were at high risk); (b) HIGH risk if three or more domains were at high risk; (c) UNCLEAR RISK in all other cases. For each comparison, the histogram was interpreted according to a "Majority risk of bias" rule;
- Across-studies bias was considered "undetected" when was not possible to evaluate the risk of publication bias;
- Indirectness: the histogram was interpreted according to a "Majority risk of bias" rule;
- Imprecision: risk ratio between 0.667 to 1.5 was considered as a clinically important size of effect;
- Heterogeneity: risk ratio between 0.667 to 1.5 was considered as a clinically important size of effect;
- Incoherence: for all the comparisons for which only a direct or indirect estimation was available (Inconsistency measures: Not applicable) we reported "some concern".

Within-study bias

The bar chart shows the contributions of each piece of study to the network estimate.
Green=low risk; yellow=unclear risk; red=high risk




bromperidol LAI:paliperidone LAI-1
bromperidol LAI:paliperidone LAI-3
bromperidol LAI:pipothiazine LAI
bromperidol LAI:risperidone LAI
bromperidol LAI:zuclopenthixol_clop LAI
flupenthixol LAI:olanzapine LAI
flupenthixol LAI:paliperidone LAI-1
flupenthixol LAI:paliperidone LAI-3
flupenthixol LAI:placebo
flupenthixol LAI:risperidone LAI
flupenthixol LAI:zuclopenthixol_clop LAI
fluphenazine LAI:olanzapine LAI
fluphenazine LAI:paliperidone LAI-1
fluphenazine LAI:paliperidone LAI-3
fluphenazine LAI:risperidone LAI
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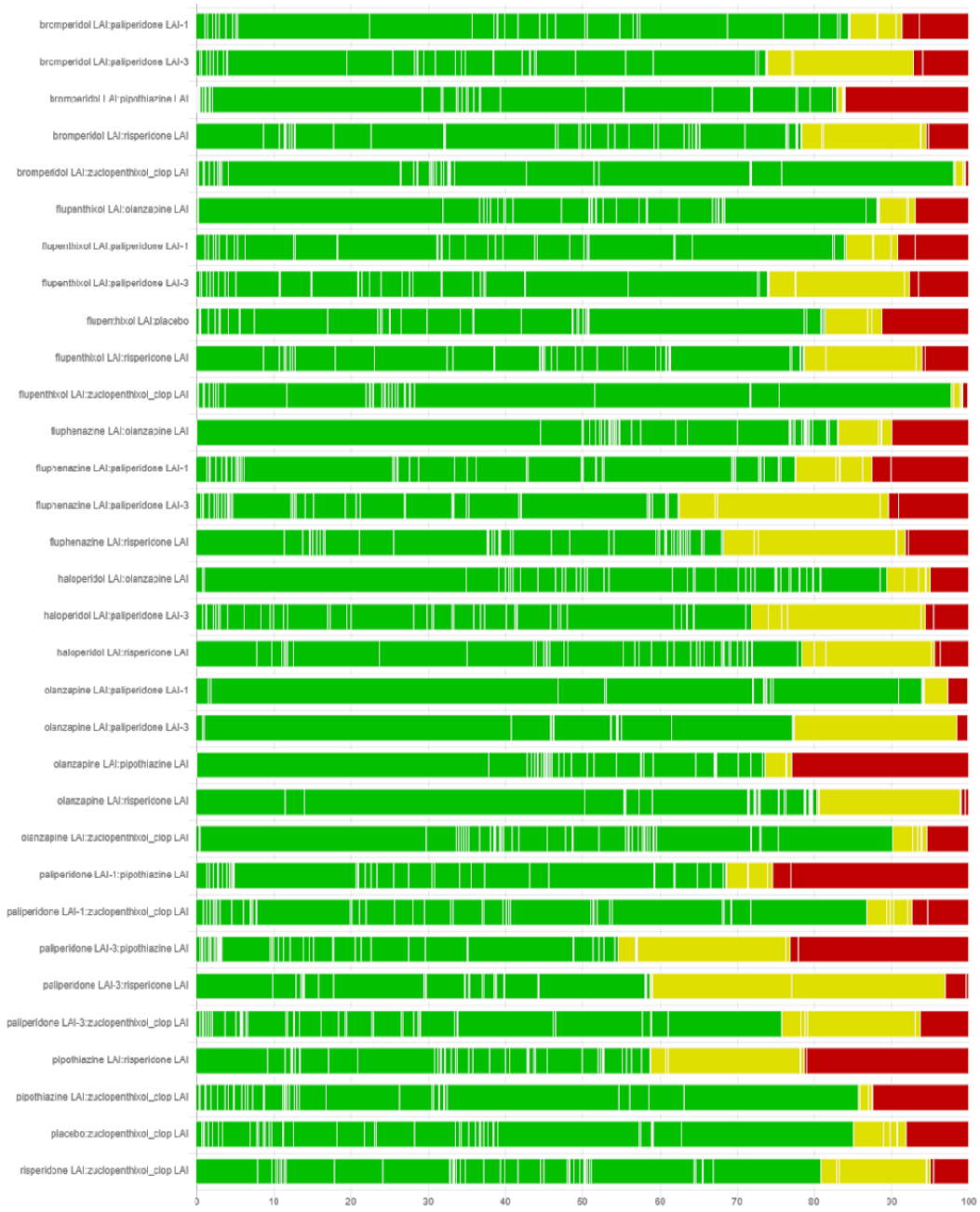
90
100

Indirectness

The bar chart shows the contributions of each study to the network estimate.
Green=low risk; yellow=unclear risk; red=high risk



Final report (GRADE table)

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
aripiprazole LAI:paliperidone LAI-1	2	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
aripiprazole LAI:placebo	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
bromperidol LAI:fluphenazine LAI	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
bromperidol LAI:haloperidol LAI	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
bromperidol LAI:placebo	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
flupenthixol LAI:fluphenazine LAI	2	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
flupenthixol LAI:haloperidol LAI	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
flupenthixol LAI:pipothiazine LAI	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
fluphenazine LAI:haloperidol LAI	5	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
fluphenazine LAI:pipothiazine LAI	7	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low
fluphenazine LAI:placebo	9	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
fluphenazine LAI:zuclopenthixol_clop LAI	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
haloperidol LAI:paliperidone LAI-1	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
haloperidol LAI:pipothiazine LAI	1	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
haloperidol LAI:placebo	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	Major concerns	Very low
haloperidol LAI:zuclopenthixol_clop LAI	1	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Low

olanzapine LAI:placebo	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
paliperidone LAI-1:paliperidone LAI-3	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
paliperidone LAI-1:placebo	2	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
paliperidone LAI-1:risperidone LAI	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
paliperidone LAI-3:placebo	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
pipothiazine LAI:placebo	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
placebo:risperidone LAI	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
aripiprazole LAI:bromperidol LAI	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
aripiprazole LAI:flupenthixol LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:fluphenazine LAI	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
aripiprazole LAI:haloperidol LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
aripiprazole LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:flupenthixol LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:paliperidone LAI-1	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
bromperidol LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:paliperidone LAI-1	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:placebo	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
flupenthixol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
fluphenazine LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
fluphenazine LAI:paliperidone LAI-1	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
fluphenazine LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
fluphenazine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
haloperidol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
haloperidol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
haloperidol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
olanzapine LAI:paliperidone LAI-1	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:paliperidone LAI-3	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-1:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-1:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-3:pipothiazine LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-3:risperidone LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-3:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
pipothiazine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
pipothiazine LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
placebo:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
risperidone LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low

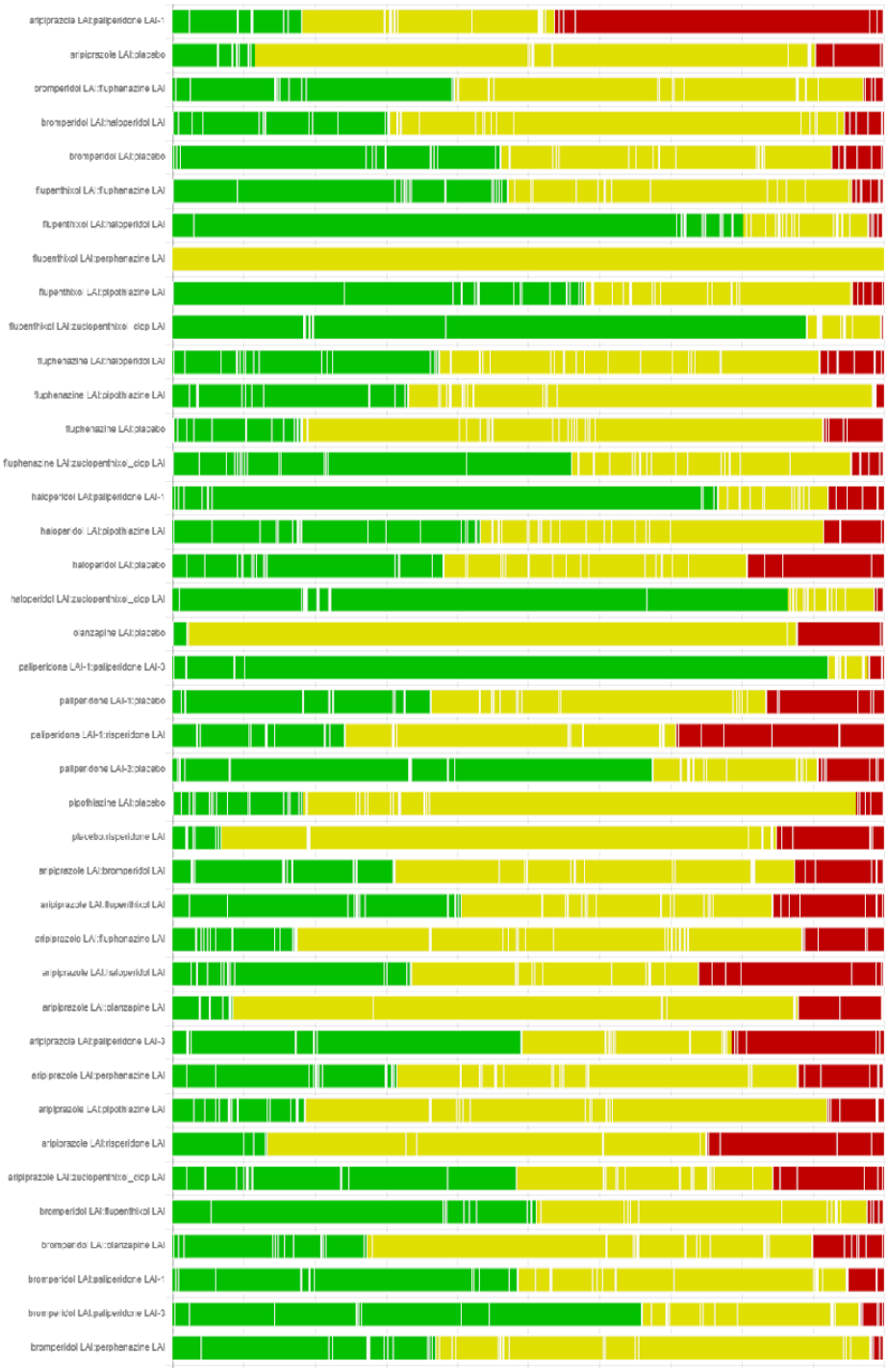
Outcome: acceptability (all-cause discontinuation)

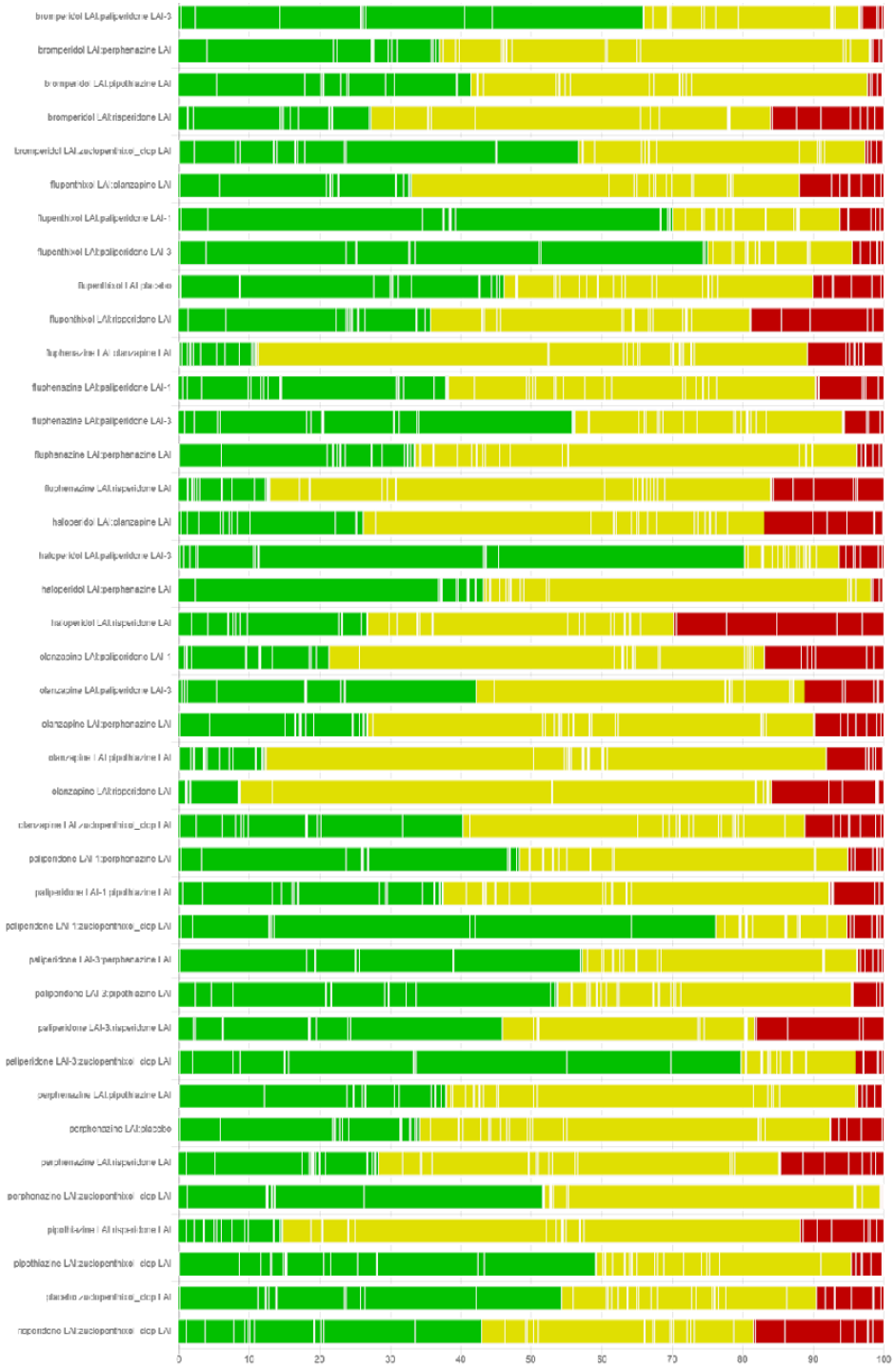
The analysis of the certainty of the evidence was performed with the online application CINeMA, which follows the principles of the GRADE methodology. The following criteria were applied:

- Within-study bias: the "overall" risk of bias of each study was calculated as follows: (a) LOW risk if four or more domains of the Cochrane RoB were at low risk (even if three were at high risk); (b) HIGH risk if three or more domains were at high risk; (c) UNCLEAR RISK in all other cases. For each comparison, the histogram was interpreted according to a "Majority risk of bias" rule;
- Across-studies bias was considered "undetected" when was not possible to evaluate the risk of publication bias;
- Indirectness: the histogram was interpreted according to a "Majority risk of bias" rule;
- Imprecision: risk ratio between 0.667 to 1.5 was considered as a clinically important size of effect;
- Heterogeneity: risk ratio between 0.667 to 1.5 was considered as a clinically important size of effect;
- Incoherence: for all the comparisons for which only a direct or indirect estimation was available (Inconsistency measures: Not applicable) we reported "some concern".

Within-study bias

The bar chart shows the contributions of each piece of study to the network estimate.
Green=low risk; yellow=unclear risk; red=high risk

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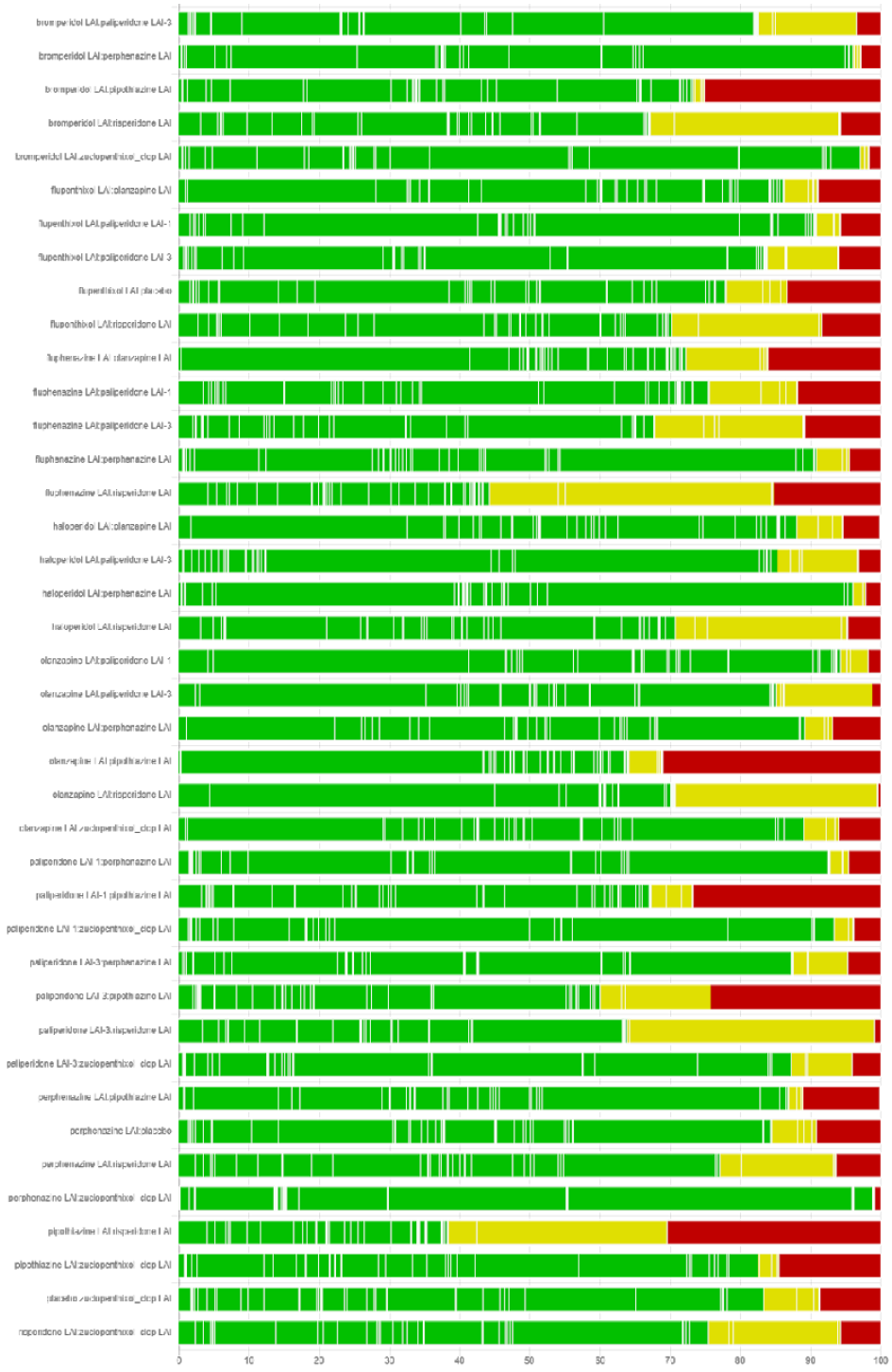
bromperidol LAI:zuclopenthixol_clcp LAI
flupenthixol LAI:olanzapine LAI
flupenthixol LAI:paliperidone LAI-1
flupenthixol LAI:paliperidone LAI-3
flupenthixol LAI:placebo
flupenthixol LAI:risperidone LAI
fluphenazine LAI:olanzapine LAI
fluphenazine LAI:paliperidone LAI-1
fluphenazine LAI:paliperidone LAI-3
fluphenazine LAI:perphenazine LAI
fluphenazine LAI:risperidone LAI
haloperidol LAI:olanzapine LAI
haloperidol LAI:paliperidone LAI-3
haloperidol LAI:perphenazine LAI
haloperidol LAI:risperidone LAI
olanzapine LAI:paliperidone LAI-1
olanzapine LAI:paliperidone LAI-3
olanzapine LAI:perphenazine LAI
olanzapine LAI:pipothiazine LAI
olanzapine LAI:risperidone LAI
olanzapine LAI:zuclopenthixol_clcp LAI
paliperidone LAI-1:perphenazine LAI
paliperidone LAI-1:pipothiazine LAI
paliperidone LAI-1:zuclopenthixol_clcp LAI
paliperidone LAI-3:perphenazine LAI
paliperidone LAI-3:pipothiazine LAI
paliperidone LAI-3:risperidone LAI
paliperidone LAI-3:zuclopenthixol_clcp LAI
perphenazine LAI:pipothiazine LAI
perphenazine LAI:placebo
perphenazine LAI:risperidone LAI
perphenazine LAI:zuclopenthixol_clcp LAI
pipothiazine LAI:risperidone LAI
pipothiazine LAI:zuclopenthixol_clcp LAI
placebo:zuclopenthixol_clcp LAI
risperidone LAI:zuclopenthixol_clcp LAI
0
10
20
30
40
50
60
70
80
90
100

Indirectness

The bar chart shows the contributions of each study to the network estimate.
Green=low risk; yellow=unclear risk; red=high risk



Final report (GRADE table)

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
aripiprazole LAI:paliperidone LAI-1	2	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Low
aripiprazole LAI:placebo	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
bromperidol LAI:fluphenazine LAI	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
bromperidol LAI:haloperidol LAI	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
bromperidol LAI:placebo	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
flupenthixol LAI:fluphenazine LAI	3	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
flupenthixol LAI:haloperidol LAI	1	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
flupenthixol LAI:perphenazine LAI	1	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:pipothiazine LAI	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate

flupenthixol LAI:zuclopenthixol_clop LAI	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
fluphenazine LAI:haloperidol LAI	7	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
fluphenazine LAI:pipothiazine LAI	10	Some concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Low
fluphenazine LAI:placebo	9	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
fluphenazine LAI:zuclopenthixol_clop LAI	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
haloperidol LAI:paliperidone LAI-1	1	No concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Moderate
haloperidol LAI:pipothiazine LAI	1	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
haloperidol LAI:placebo	2	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
haloperidol LAI:zuclopenthixol_clop LAI	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
olanzapine LAI:placebo	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
paliperidone LAI-1:paliperidone LAI-3	1	No concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Moderate
paliperidone LAI-1:placebo	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
paliperidone LAI-1:risperidone LAI	1	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
paliperidone LAI-3:placebo	1	No concerns	Undetected	No concerns	No concerns	No concerns	No concerns	High
pipothiazine LAI:placebo	1	Some concerns	Undetected	Major concerns	No concerns	Some concerns	No concerns	Very low
placebo:risperidone LAI	1	Some concerns	Undetected	Some concerns	No concerns	No concerns	No concerns	Low
aripiprazole LAI:bromperidol LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
aripiprazole LAI:flupenthixol LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
aripiprazole LAI:fluphenazine LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
aripiprazole LAI:haloperidol LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
aripiprazole LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
aripiprazole LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
aripiprazole LAI:perphenazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
aripiprazole LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
aripiprazole LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
aripiprazole LAI:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:flupenthixol LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
bromperidol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
bromperidol LAI:paliperidone LAI-1	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
bromperidol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
bromperidol LAI:perphenazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
bromperidol LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
bromperidol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
bromperidol LAI:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
flupenthixol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:paliperidone LAI-1	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
flupenthixol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
flupenthixol LAI:placebo	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
flupenthixol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
fluphenazine LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
fluphenazine LAI:paliperidone LAI-1	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
fluphenazine LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
fluphenazine LAI:perphenazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
fluphenazine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Low
haloperidol LAI:olanzapine LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
haloperidol LAI:paliperidone LAI-3	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
haloperidol LAI:perphenazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
haloperidol LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
olanzapine LAI:paliperidone LAI-1	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low

olanzapine LAI:paliperidone LAI-3	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:perphenazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
olanzapine LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
olanzapine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
olanzapine LAI:zuclopenthixol_clop LAI	0	Some concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Very low
paliperidone LAI-1:perphenazine LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-1:pipothiazine LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
paliperidone LAI-1:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
paliperidone LAI-3:perphenazine LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
paliperidone LAI-3:pipothiazine LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
paliperidone LAI-3:risperidone LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
paliperidone LAI-3:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Some concerns	Some concerns	Some concerns	Very low
perphenazine LAI:pipothiazine LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
perphenazine LAI:placebo	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
perphenazine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
perphenazine LAI:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Major concerns	No concerns	Some concerns	Very low
pipothiazine LAI:risperidone LAI	0	Some concerns	Undetected	No concerns	No concerns	Some concerns	Some concerns	Very low
pipothiazine LAI:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low
placebo:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	No concerns	No concerns	Some concerns	Moderate
risperidone LAI:zuclopenthixol_clop LAI	0	No concerns	Undetected	No concerns	Some concerns	No concerns	Some concerns	Low