C.8	Risperidone (oral) – addition of square box – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Schizophrenia is a wide mental and public health issue, causing huge disease burden. The treatment coverage rate is low, and relapse rate is high. The treatment challenges are many, but treatment adherence and individual differences play important roles on the prognosis. Difference patients with schizophrenia may respond differently for different antipsychotics in terms of side effects and efficacy. Unfortunately, only one SGA (risperidone) was on list of the WHO Model List of Essential Medicines (EML), section 24.1 “Medicines for mental and behavioural disorders”. Although risperidone is supported by evidence, some individuals might not benefit from this medication, or experience adverse events, requiring an alternative treatment. The applicants proposed the addition of a “restricted” square box symbol to risperidone to the core list of EML. Medicines proposed in treatment of psychotic disorders include aripiprazole, olanzapine, paliperidone, and quetiapine as therapeutic alternatives. The major evidence supporting the propose are that according to the most recent, high-quality meta-analytical evidence on the acute and maintenance treatment of schizophrenia and other chronic psychoses, most oral SGAs are similarly effective and tolerable, but individual variation is huge. Therefore, practitioners should be tailoring the choice of antipsychotic treatment based on individual characteristic, weighing expected benefits and harms and more SGAs should be available in the WHO list mentioned above.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: It has been estimated that about 24 million people in the world have schizophrenia. The prevalence of schizophrenia ranges from 0.2 to 0.4% across countries, while its incidence was found to be 18.7 per 100 000 person-years. Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which specifically to schizophrenia-spectrum disorders. Schizophrenia is also associated with relevant direct and indirect health care costs, and it is considered the most costly mental health condition per person globally. People with schizophrenia have a reduced life expectancy compared to the general population, calculated to be around 15-20 years. Unfortunately, the median value for treatment coverage in low and middle-income countries (LMIC) has been estimated around 30%. This suggests that roughly two thirds (70%) of people with schizophrenia-spectrum disorders in LMICs do not receive adequate treatment. According to data from large early psychosis treatment programs, most individuals at their first episode of psychosis will respond to a combination of pharmacological and psychosocial treatment, reaching functional recovery. However, most of them (up to 65%) will have at least one relapse, often related to treatment inefficacy, poor treatment adherence, or both. Treatment adherence is a major issue related to the relapse. Up to half individuals suffering from schizophrenia may not take their medications as prescribed, increasing the risk of relapse. Both clinical response and individual vulnerability to adverse events are highly heterogeneous among individuals, so it is necessary to have more SGAs in the WHO list for the different needs from patient side. All antipsychotics are equally effective and tolerable for individual patients and need more SGAs in the WHO list. Therefore, practitioners should be tailoring the choice of antipsychotic treatment based on individual characteristic, weighing expected benefits and harms and more antipsychotics should be available for the different needs from patient side.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The proposed antipsychotics including aripiprazole, olanzapine, paliperidone, and quetiapine as alternative medicine for treatment of schizophrenia are belong to Second-generation (or "atypical") antipsychotics (SGAs). SGAs are generally indicated as group of medications with: (a) relatively lower affinity for D2/3 receptors, and possibly a higher dissociation rate constant compared to FGAs, and consequently lower risk of extrapyramidal symptoms; (b) an higher ratio of binding to the serotonin 2A receptor (5-HT2A) relative to binding to the dopamine D2/3 receptor; (c) a preferential affinity for the limbic, as opposed to motor, areas of the striatum. However, medications currently labelled as SGAs are heterogeneous in both chemical, pharmacological and clinical terms. Huhn and colleagues performed a network meta-analysis including both placebo-controlled and head-to head randomized controlled trials comparing 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia. Overall, they included 402 RCTs and 53 463 participants. Most antipsychotics (26 over 31, 81%) outperformed placebo, with Standardized Mean Differences (SMDs) ranging between -0.89 (clozapine) to -0.26 (brexpiprazole). Effect sizes and 95% Credible Intervals (95% CrI) were largely overlapping. Most of these comparisons barely reach statistical significance and, most importantly, differences are clinically negligible (Cohen's d < 0.2). In general, differences between risperidone and other SGAs were clinically and statistically very small in terms of acceptability of treatments (all-cause discontinuation). In conclusion, SGAs are performing better than placebo in terms of efficacy for both acute and maintenance treatment, better/no worse than placebo in terms of acceptability (overall dropout rate) for both acute and maintenance treatment and having a moderate-to-high certainty of evidence according to the CINeMA appraisal for the majority (⩾3/4) of these outcomes.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Generally speaking, the side effects of SGAs including: metabolic (weight gain and diabetes etc.); extrapyramidal (including akathisia, dyskinesia and dystonia); cardiovascular (including prolonging the QT interval); hormonal (including increasing plasma prolactin); other (including unpleasant subjective experiences). But different SGAs have different side effect profiles. For example, olanzapine and quetiapine produced more problems relating metabolic syndrome than aripiprazole, risperidone. On contrast, aripiprazole and risperidone produce more extrapyramidal symptoms (EPS), and Risperidone commonly cause hyperprolactinemia.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension cardiac arrhythmia, even sudden cardiac death in some rare cases. Health providers, esp family doctors should understand the individual adverse effect profiles of these medications. They should be vigilant for the occurrence of adverse effects, be willing to adjust or change medications as needed. Healthcare professionals and service users should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. S
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☐ Not applicable Comments: Special training should be provided health professionals on the titration and adverse effects monitoring, and the patients are recommended to take lab tests regularly on liver and kidney functioning, metabolism and endocrinology etc.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable Comments: In resource-limited countries, the use of FGAs is prevalent, and SGAs are usually reserved in case of serious collateral effects or inefficacy. There is debate around whether a routine use of SGAs in these countries could be favorable in terms of medical-economic resources as compared to FGAs, despite their higher procurement cost. Current evidence on the matter is scant and controversial. Among SGAs, olanzapine and risperidone often appear to have the most favorable cost-effectiveness profile. The patents of proposed antipsychotics all had expired, many generic versions of these antipsychotics are now available worldwide. So, the availability and affordability of the proposed medicines are generally acceptable.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: In psychiatric clinical practice, SGAs are also used in other mental diseases, such as bipolar disorder, depressive disorders, OCD etc.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: The proposed medicines are recommended in mhGAP, version. With the exception of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) guidelines, which clearly indicate SGAs as the first-choice treatment (and particularly, amisulpride, aripiprazole, risperidone, quetiapine, ziprasidone), most clinical guidelines do not provide indication on which antipsychotic to choose, generally agreeing on the importance of tailoring the choice on individual patients' characteristics, actively involving patients and caregivers in a shared decision-making process.