F.8	Paliperidone palmitate –3-month long-acting injection – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Schizophrenia is a chronic, complex, and significantly disabling mental disorder that often requires lifelong pharmacological treatment. Despite the need for ongoing treatment, it is estimated that two thirds of schizophrenia patients are partially or fully noncompliant with their antipsychotic medications, which results in poor outcomes including increased hospitalizations, relapse risk, poorer prognosis, and risk of harm to self and others. On the current WHO Model List of Essential Medicines (22nd list), the core list of medicines for psychotic disorders includes chlorpromazine and haloperidol as representative first-generation oral antipsychotics (OAPs) and risperidone (Paliperidone is the major active metabolite of risperidone) as the representative second-generation OAP. Long-acting injectable antipsychotics include fluphenazine (decanoate or enanthate) as a representative first-generation long-acting injection (LAI) and paliperidone palmitate 1-month long-acting injection (PP1M) as a representative second-generation LAI. Risperidone LAI was included as a therapeutic alternative to PP1M. The applicant proposed to include PP3M for treatment of adults with schizophrenia to the WHO Model List of Essential Medicines. The ease of use of PP3M is an important consideration for both patients and caregivers. Patients who treated with PP3M or swich from PP1M have less frequent injections, less administration and planning, and less focus on the illness longer injection intervals could reduce travel burden and cost while maintaining psychiatric stability in patients with schizophrenia. A company-sponsored noninferiority study of PP3M showed that PP3M was noninferior to PP1M as measured by the proportion of subjects who remained relapse free after 48 weeks (relapse rates of 8.1% with PP3M vs 9.2% with PP1M). PP3M is commercially available as a prefilled syringe not requiring refrigeration and provides treatment. Clinical data suggests that PP3M, on average, protects patients from relapse for a median time of 274 days after a single dose. These benefits are valuable for patients who have limited access to psychiatric care, and who are homeless in communities, etc. In conclusion, the advantages of PP3M compare with PP1M are: less injection per year, less time needed for drug administration, one dose of PP3M costs as much as three doses of PP1M, but costs for administration are about 1/3, and finally, more flexible acceptable delay between two administrations of PP3M. However, due to the slow-release profile, treatment with PP3M is not intended for use in acutely symptomatic patients or in patients who are immediately transitioning from oral or other (non-PP1M) LAI antipsychotic therapy. And patients must already be adequately treated with PP1M at a stable dose prior to switching to PP3M in order to establish a consistent maintenance dose.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Schizophrenia is a complex, significantly disabling mental disorder, with typical onset in late adolescence or early adulthood affecting nearly 24 million people globally. The incident cases and DALYs of schizophrenia increased from 1990 to 2017, reaching 1.13 million persons. Compared with 1990, the incident cases and DALYs had increased by 37% and 62%, respectively. The treatment compliance is one of challenge for the treatment gap and related high relapse rate. In a study of 50 low- and middle-income countries (LMIC), about two thirds of individuals with schizophrenic disorders are inadequately treated, with a treatment gap ranging from a high of 89% in the lower-income countries to about two thirds in the lower-middle-income and upper-middle-income countries (69% and 63%, respectively). The treatment compliance is one of challenge for the treatment gap and related high relapse rate. People with schizophrenia have a reduced life expectancy compared with the general population, of about 15 years. While mental health disorders can reduce life expectancy, reduced life expectancy also relates to the burden of physical diseases, for example, cardiovascular disease.
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 network meta-analysis by Ostuzzi (2021b) was the basis of the clinical evidence in the application to the 23rd WHO Expert Committee on Selection and Use of Essential Medicines for inclusion of PP1M on the WHO EML. The meta-analysis included 78 clinical studies in 11,505 adults with nonaffective psychoses. Results showed that most LAIs were similarly effective and acceptable, but paliperidone palmitate (PP1M and PP3M), olanzapine, and aripiprazole had the highest effect sizes and certainty of evidence for both relapse prevention and overall acceptability. The noninferiority study included 1,429 adults with schizophrenia (52% from middle-income countries and 48% from high-income countries) who received open-label PP1M for 17 weeks followed by randomization, if clinically stable, to double-blind treatment with PP3M (n=504) or PP1M (n=512). The primary analysis for efficacy found that PP3M was noninferior to PP1M as measured by the proportion of subjects who remained relapse free after 48 weeks (relapse rates of 8.1% with PP3M vs 9.2% with PP1M based on Kaplan-Meier estimates; difference in relapse-free rate, with the lower bound of the 95% CI being larger than the 15% noninferiority margin. Efficacy of PP3M was also evaluated against placebo in one double-blind (DB) RCTs. The study was stopped by an independent data monitoring committee for greater efficacy of PP3M compared to placebo: during the DB phase, 29% of patients in the placebo group experienced a relapse event against 9% in the group receiving PP3M. The results in real world study of the all-cause discontinuation analysis showed that the likelihood of treatment continuation for patients receiving LAIs was generally higher than for those receiving OAPs. PP3M had the highest 1- and 1.5-year continuation rates across all antipsychotics (LAIs and OAPs). The discontinuation rate did not reach 50% during the 1.5-year observation period for patients on PP3M.

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: Overall, the types and rates of clinically significant AEs of special interest in subjects treated with PP3M were consistent with the safety profile of PP1M, the occurrence of NMS, tardive dyskinesia/EPS, QT interval prolongation, hyperglycemia and diabetes mellitus, weight gain, and prolactin-related AEs and hyperprolactinemia, as well as discontinuations due to these AEs were no significant different between the groups. Injections were well tolerated, and the injection site pain were low and mild, none of the injection site-related treatment-emergent adverse events (TEAEs) were reported as a serious AE during the study. In a 1-year retrospective and prospective observational cohort study in 90 patients with schizophrenia spectrum disorders, the incidence of increased appetite and weight was significantly higher for PP3M (40.9%) and PP1M (76.5%) compared with haloperidol decanoate (17.6%). There were no significant differences between treatments in sedation, EPS, decreased libido, or BMI. All the discontinuations in the PP3M group (15.4% of enrolled patients) were due to patient refusal; in the PP1M group the discontinuations were due to patient refusal (7.4%), side effects (3.7%) and medical indications (7.4%), and in the haloperidol decanoate group were due to ineffective treatment (2.7%), medical indications (2.7%), and death (2.7%).
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
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: it is recognized that optimal management of schizophrenia requires the integration of both medical and psychosocial interventions, and that such interventions should not be seen as competing approaches but, in most cases, as necessary and complementary interventions to improve clinical symptoms, functional outcome, and quality of life .

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Schizophrenia is a costly disease due to its early onset among young adults, chronic nature, and high morbidity and mortality. The economic burden is substantial and can be attributed to many sources. The direct costs of schizophrenia include inpatient/outpatient care, drug costs, treating and managing side effects and comorbidities, rehabilitation, and social welfare administration. The indirect costs of schizophrenia include unemployment, reduced productivity at work, premature mortality, inability to live independently, and its financial impacts to family life. Additionally, in resource-limited countries, where the number of specialized health care providers is limited, patients with schizophrenia must travel long distances to access care, thereby incurring additional expenses. One study conducted in Spain on the cost-effectiveness of PP3M for chronic schizophrenia showed the expected cost was lower with PP3M (4780 Euro) compared with PP1M (5244 Euro). PP3M had the few relapse, hospitalization, and emergency room visits, compared with PP1M. Another study in Netherland showed similar results, the expected cost was lowest with PP3M, followed by PP1M, haloperidol long-acting therapy, risperidone microspheres and oral olanzapine. For less resource countries, liking Rwanda and South Africa, despite potentially higher drug acquisition cost, PP3M/PP1M are cost-saving for maintenance treatment of schizophrenia. So, patients who require long-acting therapy, PP3M appears to be a good alternative anti-psychotic treatment.
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: Generic PP1M (Teva GmbH, Germany) has been approved in the European Union (EU) since late 2021 and is now marketed in France and Germany. A generic PP3M has not been approved in the European Union. Viatris™, a global pharmaceutical company, has filed applications for complex generic formulations of PP1M and PP3M that are currently under regulatory review. In 2020/2021, Viatris filed 3 applications in the United States for various strengths of generic PP3M, but approval is currently delayed to 2023/2024.

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: In the WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological, and substance use disorders, it is recommended that depot antipsychotics can be offered instead of oral medication as part of a treatment plan in patients with psychotic disorders (including schizophrenia) requiring long-term antipsychotic treatment. The WHO mhGAP also advises that depot/LAI antipsychotic medication may be considered when adherence to treatment is unsatisfactory. Guidelines from the American Psychiatric Association, British Association for Psychopharmacology, Chinese Psychiatry Society, Canadian Health Care System, National Institute for Health and Care Excellence, Royal Australian and New Zealand College of Psychiatrists, and Scottish Intercollegiate Guidelines Network (SIGN) suggest or recommend that individuals with schizophrenia requiring long-term antipsychotic treatment, those who request depot/LAI medication, and those with medication adherence difficulties should be offered maintenance treatment with depot/LAI antipsychotic medication.