A.29	Olanzapine – psychotic disorders – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Olanzapine IM injection may be a useful treatment option for patients with acute agitation and psychosis who require rapid relief of symptoms or who have difficulty adhering to oral medication. The rapid onset of action and effectiveness of olanzapine IM injection may reduce the need for physical restraints, which can be traumatic for patients and increase the risk of injury. Olanzapine IM injections are generally as effective and acceptable as haloperidol IM, with a more tolerable profile in terms of motor symptoms, including acute dystonia and other extrapyramidal symptoms. Olanzapine IM is included in many national pharmacopoeias and is available as generic medication in many countries. Psychotic disorders such as schizophrenia can have a significant impact on the affected individuals and their families, and effective treatments are essential to improving their quality of life. Therefore, olanzapine injection can be considered to address a relevant public health need for the management of psychotic disorders. Currently, the EML includes injectable intramuscular immediate-release formulations of two first generation antipsychotics (FGAs): chlorpromazine and haloperidol. Currently, the EML does not include immediate-release injectable formulations of second-generation antipsychotics (SGAs) but only includes oral risperidone (since 2013) and long-acting injectable paliperidone (since 2021 and with a restricted square box indicating risperidone as therapeutic alternative).
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The burden of acute psychosis and agitation can be significant, impacting individuals, families, and society. Patients experiencing acute agitation and psychosis can pose a significant risk to themselves and those around them including injuries, hospitalizations, and even death. Acute psychosis and agitation can significantly impair an individual's quality of life and ability to maintain relationships with others. The treatment of acute psychosis and agitation can be costly, particularly if hospitalization or emergency care is required. Individuals with acute psychosis and agitation may require support from family members or caregivers, which can place a significant burden on the caregivers. Up to 20% of psychiatric emergency visits might involve agitated individuals with schizophrenia. Olanzapine IM injection can provide rapid relief of symptoms, reducing the risk of harm to the individual and others. By providing a rapid and effective treatment option, olanzapine IM injection can help reduce the burden on emergency services and improve patient outcomes.

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: There is adequate evidence to support the efficacy and effectiveness of olanzapine IM injection for the treatment of acute agitation associated with psychotic disorders. According to several clinical trials and systematic reviews, olanzapine IM can rapidly and effectively control agitation and aggression in patients with schizophrenia and bipolar disorder and olanzapine IM was found to be more effective than placebo, haloperidol, and lorazepam in reducing agitation and achieving clinical stabilization. Moreover, olanzapine IM has some advantages over other antipsychotic medications in terms of onset of action, tolerability, and patient preference. It can produce a rapid sedative effect within 30 minutes and maintain therapeutic blood levels for up to 24 hours, allowing for a single injection to control acute agitation. Also, olanzapine IM has a lower risk of extrapyramidal symptoms, such as tremors, rigidity, and akathisia, compared to other typical antipsychotics. Overall, olanzapine IM is a well-established and effective treatment option for acute agitation associated with psychotic disorders.
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: There is evidence indicating that the olanzapine IM injection is generally safe and well-tolerated for the management of acute agitation associated with psychotic disorders. Some of the common adverse effects associated with the olanzapine IM injection include sedation, weight gain, extrapyramidal symptoms, and orthostatic hypotension. More serious but rare adverse events reported include neuroleptic malignant syndrome, tardive dyskinesia, and metabolic changes such as hyperglycemia and dyslipidemia, therefore, need careful monitor of patients receiving olanzapine IM injection, especially those with risk factors or predisposing conditions such as history of hypersensitivity or previous adverse reactions to olanzapine or other antipsychotic medications, cardiovascular disease or cerebrovascular disease.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Metabolic changes (weight gain, dyslipidemia, and hyperglycemia) need regular monitoring. Orthostatic hypotension leading to dizziness and fainting requires regular BP monitoring. Olanzapine can cause extrapyramidal symptoms (EPS) such as akathisia, dystonia, and parkinsonism. Olanzapine can cause sedation, which may impair a patient's ability to perform activities that require alertness such as driving or operating heavy machinery. Olanzapine can cause anticholinergic effects such as dry mouth, constipation, and urinary retention. Adverse effects of concern that may require special monitoring for neuroleptic malignant syndrome (NMS), though rare.

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: No special monitoring is usually required except for adverse effects, sedation, and vitals. Olanzapine injection should only be used in patients who are acutely agitated or disturbed and require rapid sedation. It should not be used as a maintenance treatment for psychosis. Requires dosage adjustment in patients with hepatic impairment. Need precautions in patients with cardiovascular disease and diabetes, as it may cause orthostatic hypotension and hyperglycemia. It should be used with caution in elderly patients as they are more susceptible to adverse effects, such as sedation, hypotension, and extrapyramidal symptoms. The safety of olanzapine injection has not been established in pregnant and lactating women.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Access to olanzapine may also be limited by the availability of the medication in certain regions or the lack of trained healthcare personnel who can administer it effectively. In some settings, there may be regulatory or logistical barriers to the distribution and administration of injectable medications like olanzapine.
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: Olanzapine IM injection is approved for use in several countries, including the US, Canada, and various European countries. However, the registration and approval process for medications can vary between countries and regulatory agencies, and there may be specific issues related to the registration of olanzapine. In some countries, olanzapine may be available as a prescription medication, while in others, it may require additional approvals or may not be available at all. The registration process may impact the availability, cost, and accessibility of the medication in different settings. Generic formulations of olanzapine are not available yet. The inclusion of olanzapine will therefore attract additional manufacturers, facilitate importations, alert manufacturers about the need for local registrations, better allow for competition between manufacturers to improve accessibility overall, particularly in low-and middle-income countries.

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: Among injectable antipsychotics, haloperidol and chlorpromazine are highly represented in National Medicines List/Formulary/Standard Treatment Guidelines, whereas second-generation antipsychotics are hardly ever included. Most clinical guidelines do not provide indication on which antipsychotic to choose, generally agreeing in the importance of tailoring the choice on individual patients' characteristics, actively involving patients and caregivers in a shared decision-making process.