A.25	Molnupiravir – COVID-19 – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Molnupiravir is the oral prodrug of a nucleoside analog that affects the copying of the SARS-CoV-2 genome and leads to production of mutated and non-functional virus RNA. It is given orally twice daily for 5 days as early as possible in clinical infection and ideally within 5 days of the onset of symptoms. It is active in vitro on Alpha, Beta, Delta and Omicron variants. The evidence summary in the WHO COVID-19 Living Guideline noted that six trials with 4796 patients were included for analysis. There was moderate level evidence for decreased hospitalisation, low level evidence for reduction in mortality and moderate for time to symptom resolution. There was a probable reduction in hospitalisation of 27/1000 of the highest risk patients. The drug is well tolerated and in the evidence summary, the rates of adverse events in patients treated with molnupiravir were no different than in placebo or active agent arms. Molnupiravir was noted to be mutagenic in vitro, but with no evidence of mutagenicity in animal models. It is likely to be present in breast milk. Higher drug exposure was associated with embryofoetal death and teratogenicity in rats. It should not be given in pregnancy, or to breast feeding mothers with birth control recommended for men for 3 months after treatment. The concern of genotoxicity is likely to be higher in younger patients. WHO COVID-19 Living Guideline has a conditional approval for the use of molnupiravir for patients with non-severe infection at highest risk of hospitalisation (excluding pregnant and breastfeeding women and children).
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: COVID-19 has infected over 600 million people globally, with an estimated over 6 million deaths.
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 evidence summary in the WHO COVID-19 Living Guideline noted that six trials including 4796 patients were included for analysis. There was moderate level evidence for decreased hospitalisation, low level evidence for reduction in mortality and moderate evidence for time to symptom resolution.

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: The drug is well tolerated and in the evidence summary, the rates of adverse events in patients treated with molnupiravir were no different than in placebo or active agent arms.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Molnupiravir was noted to be mutagenic in vitro, but with no evidence of mutagenicity in animal models. It is likely to be present in breast milk. Higher drug exposure was associated with embryofoetal death and teratogenicity in rats. It should not be given in pregnancy, or to breast feeding mothers with birth control recommended for men for 3 months after treatment. The concern of genotoxicity is likely to be higher in younger patients.
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: Rapid viral diagnostic tests should be available to confirm the diagnosis.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: The ACT-Accelerator plan is pushing generic product availability.
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: The Medicines Patent Pool holds a licensing agreement to provide molnupiravir in 105 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: WHO COVID-19 Living Guideline has a conditional approval for the use of molnupiravir for patients with non-severe Covid-19 at highest risk of hospitalisation (excluding pregnant and breastfeeding women and children).