A.27	Nirmatrelvir and ritonavir – COVID-19 – EML and EMLc
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Nirmatrelvir is a SARS-CoV-2 protease inhibitor, inhibiting viral replication. It is an orally active analogue of an intravenous prodrug. It is co-administered with ritonavir, a well-established HIV protease inhibitor, which boosts the levels of nirmatrelvir without any anti-viral activity. It is dosed twice daily for five days in adults and for children over 12 years of age. Treatment should be started ideally within 5 days of symptom onset. The Covid-19 WHO Living Guideline evidence summary included data from two trials with 3100 patients in the meta-analysis. There was low level evidence of no important difference in mortality, with high uncertainty for mechanical ventilation. There was moderate level evidence of around 30/1000 fewer hospital admissions in the trial population, and around 50/1000 fewer admissions in the high-risk population. A Cochrane review noted significantly higher taste and GI symptoms in patients receiving nirmatrelvir (given with a higher dose of ritonavir than used in HIV patients) than placebo with higher rates of drug discontinuation due to adverse events. In high-risk populations (age >60 years, unvaccinated, immunosuppressed, chronic disease) there was a strong recommendation in favour of the drug.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Covid-19 is estimated to have caused over 600 million infections with over 6 million deaths globally.
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 Covid-19 WHO Living Guideline evidence summary included data from two trials with 3100 patients in the meta-analysis. There was low level evidence of no important difference in mortality, with high uncertainty for mechanical ventilation. There was moderate level evidence of around 30/1000 fewer hospital admissions in the trial population, and around 50/1000 fewer admissions in the high-risk population. In high-risk populations (age >60 years, unvaccinated, immunosuppressed, chronic disease) there was a strong recommendation in favour of the drug.

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: A Cochrane review noted significantly higher taste and GI symptoms in patients receiving nirmatrelvir (given with a higher dose of ritonavir than used in HIV patients) than placebo with higher rates of drug discontinuation due to adverse events.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: There are multiple potential drug interactions, especially through CYP3A inhibition.
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 Diagnostic Tests to confirm a Covid-19 diagnosis assists with early treatment of symptomatic disease.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: The drug is not licensed yet by the FDA for pregnant women, or children younger than 12 years.
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 ACT-Accelerator is pushing for generic product availability. The MPP holds a licence agreement for 95 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: The WHO Covid-19 living guideline has a strong recommendation in favour of the drug for high-risk populations (age >60 years, unvaccinated, immunosuppressed, chronic disease).