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A.25 Molnupiravir

MSF supports the inclusion of molnupiravir in the WHO Model List of Essential Medicines (EML).

Currently, there is no medicine for the treatment of patients with COVID-19 included in the EML.

Globally, as of 21 March 2023, there have been 761 071 826 confirmed cases of COVID-19, including 6 879 677 deaths, reported to WHO and a total of 13 260 401 200 vaccine doses have been administered[1].

The 2023 WHO "Therapeutics and COVID-19: living guideline" states that vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. Even in vaccinated individuals, uncertainties remain about the duration of protection and effectiveness of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants and subvariants and resistance to monotherapies. Therefore, there remains a need for more effective treatments for COVID-19[2] and further evidence on oral antiviral combination therapy in the context of resistance.

Real life evidence from big cohort studies that oral antivirals (notably Nirmatrelvir/ritonavir, also some evidence for molnupiravir) have a positive impact in preventing hospitalizations and/or deaths even among those who have received COVID-19 vaccine, if high risk[3][4]. In addition, there is some evidence

[1] WHO Coronavirus (COVID-19) Dashboard - https://covid19.who.int/

[2] Therapeutics and COVID-19: living guideline, 13 January 2023. Geneva: World Health Organization; 2023 (WHO /2019-nCoV/therapeutics/2023.1).

[3]https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e2.htm
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00011-7/fulltext
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01586-0/fulltext
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00118-4/fulltext

[4] Ronza Najjar-Debbiny, Naomi Gronich, Gabriel Weber, Johad Khoury, Maisam Amar, Nili Stein, Lee Hilary Goldstein, Walid Saliba, Effectiveness of Molnupiravir in High-Risk Patients: A Propensity Score Matched Analysis, *Clinical Infectious Diseases*, Volume 76, Issue 3, 1 February 2023, Pages 453–460, https://doi.org/10.1093/cid/ciac781

as well that some oral antivirals may decrease the risk of Long COVID (Post-COVID Condition)[5]. Furthermore, the longer-term harms (including genotoxicity, emergence of resistance, emergence of new variants) of many oral antiviral therapeutics remain unknown in the absence of clinical evidence.

Molnupiravir is an orally antiviral, originally designed as an influenza treatment, although not approved. Molnupiravir inhibits the replication of SARS-CoV-2 and was re-purposed early in development as an antiviral for SARS-CoV-2.
For patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children), the WHO "Therapeutics and COVID-19: living guideline" suggests treatment with molnupiravir (conditional recommendation). People at highest risk of hospitalization include people with older age, immunosuppression and/or chronic diseases, with lack of COVID-19 vaccination as an additional risk factor to consider. The recommended dose for molnupiravir is a twice-daily intake of an 800 mg tablet, for 5 days. Molnupiravir should be administered as soon as possible after onset of symptoms, ideally within 5 days. Molnupiravir presents the advantage of a twice daily intake, unlike remdesivir which has to be given by intravenous infusion once daily.
Molnupiravir is contra-indicated in pregnant women, breastfeeding women and in children.
If a woman of childbearing age has to be treated by molnupiravir, counselling birth control during treatment and for 4 days after the last dose of molnupiravir should be facilitated.
The longer-term harms (including genotoxicity, emergence of resistance, emergence of new variants) of molnupiravir remain unknown in the absence of clinical evidence. The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available. The unknown long-term risk of genotoxicity is likely to be higher in younger patients as compared with older patients; thus use in younger adults who are not at high risk should be limited. The 2023 WHO "Therapeutics and COVID-19: living guideline" states the need for clinical data to investigate safety and applicability concerns (including in children, lactating or pregnant women, and men; and long-term impact on mutagenesis and cancer risk).

The conclusion of the Guideline Development Group is that in patients with non-severe COVID-19 at highest risk of hospitalization, molnupiravir probably reduces admission to hospital and time to symptom resolution, and may reduce mortality.

Currently, molnupiravir is provided commercially by the patent holder. In January 2022, the Medicines Patent Pool announced that it has signed agreements with 27 generic manufacturing companies to produce low-cost versions of molnupiravir for supply in 105 low- and-middle-income countries. Two generics have been already WHO prequalified (eight are in the pre-qualification pipeline), the ACT-Accelerator Transition Plan is in place to promote generic product availability, expected from mid-2023.

[5] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2802878

MSF would like to emphasized that it is important to include molnupiravir in the EML as an oral alternative to be used when the first choice nirmatrelvir/ritonavir is not accessible or available (as access to molnupiravir is less difficult, with more generics available) or when nirmatrelvir/ritonavir cannot be used due to drug-drug interactions, which abound, particularly among older higher risk patients frequently under polypharmacy.

In light of these elements, MSF recommends that the 24th Expert Committee on the Selection and Use of Essential Medicines consider including molnupiravir in the WHO Model List of Essential Medicines.

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