International Office

140 Route de Ferney, Case Postale 1224

CH-1211 Geneva 1, SWITZERLAND

Phone: +41 (0)22 849 84 00

Fax: +41 (0)22 849 84 88

www.msf.org

A.27 Nirmatrelvir and ritonavir

MSF strongly supports the inclusion of nirmatrelvir co-administered with ritonavir (nirmatrelvir-ritonavir) in the WHO Model List of Essential Medicines (EML).

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

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]. In addition, there is some evidence as well that some oral antivirals may decrease the risk of Long COVID (Post-COVID Condition)[4]. 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.

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

Nirmatrelvir inhibits the SARS-CoV-2 protease, thereby preventing cleavage of the viral polyprotein which is needed for viral proteins to become functional. Inhibition of the protease renders the virus unable to replicate. Nirmatrelvir is co-administered with ritonavir, an HIV protease inhibitor, used in this context to boost the pharmacokinetics of nirmatrelvir but without exerting any direct antiviral activity itself. Therefore, the combination should be considered as antiviral monotherapy[2].

For patients with non-severe COVID-19 at highest risk of hospitalization, the WHO "Therapeutics and COVID-19: living guideline" makes a strong recommendation for treatment with nirmatrelvir-ritonavir. 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. For patients with non-severe COVID-19 at low risk of hospitalization the guideline suggests not to use treatment with nirmatrelvir-ritonavir.

The recommended dose for nirmatrelvir-ritonavir is a twice-daily intake of 300 mg of nirmatrelvir co-administered with 100 mg of ritonavir for 5 days. Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.
As a strong inhibitor of CYP3A4, ritonavir has the potential to interact with several medicines. Clinicians should review all medications and not use nirmatrelvir-ritonavir in patients with possible dangerous drug interactions.

In January 2023, the Guideline Development Group made an updated recommendation concerning the use of nirmatrelvir-ritonavir in breastfeeding and pregnant women with non-severe illness: given the likely benefits and residual uncertainty regarding undesirable effects, a fully informed decision-making between mother and health care provider should determine the use or non-use of nirmatrelvir-ritonavir in women with non-severe COVID-19[2].

Nirmatrelvir-ritonavir has received an US Food and Drug Administration (FDA) Emergency Use Authorization for the treatment of adults and pediatric patients (12 years of age and older weighing at least 40 kg) with a current diagnosis of mild-to-moderate COVID-19 and who are at high risk for progression to severe COVID-19, including hospitalization or death[5]. Recently, the FDA Advisory Committee has recommended full approval; the final decision will happen in May 2023[6].

The conclusion of the Guideline Development Group is that in patients with non-severe COVID-19, nirmatrelvir-ritonavir likely reduces admission to hospital. It may have little or no impact on mortality. There are no data reported for time to symptom resolution or mechanical ventilation. Nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives; has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and antibodies.

[5] Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for Paxlovid. 2022. https://www.fda.gov/media/155050/download

[6] https://www.pfizer.com/news/press-release/press-release-detail/fda-advisory-committee-votes-support-favorable-benefit-risk

Currently, nirmatrelvir-ritonavir is provided commercially by the patent holder (Pfizer). In March 2022, the Medicines Patent Pool announced that it has signed agreements with 35 generic manufacturing companies to produce low-cost, generic versions of nirmatrelvir in combination with ritonavir for supply in 95 low- and-middle-income countries. MSF would like to emphasize that the agreements signed between the Medicines Patent Pool and 35 manufacturers to produce and supply nirmatrelvir/ritonavir are a welcome step, but the signed agreement only covers 53 percent of the world's population and excludes millions of people in middle-income countries. Most Latin American countries, including Brazil, are left out of this deal, as well as other middle-income countries, such as China, Malaysia and Thailand – this will have a chilling effect on the availability of more affordable generic versions of the drug produced under this license if Pfizer is granted patents in those countries[7].

Two generics has been already WHO prequalified, four are in the prequalification pipeline and the ACT-Accelerator Transition Plan is in place to promote generic product availability (expected early 2023).

MSF would like to highlight that the EMLc is intended for use for children up to and including 12 years of age. The application states that the proposal for inclusion relates to both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children, but highlights that nirmatrelvir-ritonavir should only be used in children **over** 12 years old and that its use is not recommended in children below 12 years.

In the light on these elements, MSF urges the 24th Expert Committee on the Selection and Use of Essential Medicines to include nirmatrelvir-ritonavir in the WHO Model List of Essential Medicines and recommends that the Expert Committee evaluate the benefits and the risks of nirmatrelvir-ritonavir in the perspective of its inclusion in WHO Model List of Essential Medicines for Children.

Dr. Daniela Belen Garone

Infectious Diseases specialist and DTM&H
International Medical Coordinator

Médecins Sans Frontières | International Office

[7] https://msfaccess.org/msf-responds-medicines-patent-pool-deal-35-manufacturers-produce-covid-19-treatment
https://msfaccess.org/latin-america-how-patents-and-licensing-hinder-access-covid-19-treatments